

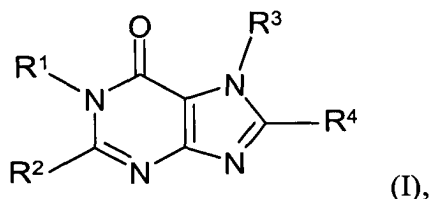
**New purine derivatives, the preparation thereof and their
use as pharmaceutical compositions**

Related Applications

Benefit of U.S. Provisional Application Serial No. 60/408,021, filed on September 4, 2002 and German application DE 102 38 477 filed August 22, 2002 is hereby claimed.

Field of the Invention

The present invention relates to substituted purines of general formula



the tautomers, the stereoisomers, the mixtures, the prodrugs thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof for the prevention or treatment of diseases or conditions associated with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof as well as processes for the preparation thereof.

In the above formula I

R¹ denotes a hydrogen atom,

a C₁₋₈-alkyl group,

a C₃₋₈-alkenyl group,

a C₃₋₄-alkenyl group which is substituted by a C₁₋₂-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl, di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl,
5 piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

a C₃₋₈-alkynyl group,

10 a C₁₋₆-alkyl group substituted by a group R_a, where

R_a denotes a C₃₋₇-cycloalkyl, heteroaryl, cyano, carboxy, C₁₋₃-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl, di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-
15 1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

a C₁₋₆-alkyl group substituted by a phenyl group, where the phenyl ring is substituted by the groups R¹⁰ to R¹⁴ and

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R¹⁰ denotes a hydrogen atom,

a fluorine, chlorine, bromine or iodine atom,

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a C₁₋₄-alkyl, hydroxy or C₁₋₄-alkyloxy group,

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a nitro, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, cyan-C₁₋₃-alkylamino, N-(cyan-C₁₋₃-alkyl)-N-(C₁₋₃-alkyl)-amino, C₁₋₃-alkyloxy-carbonyl-C₁₋₃-alkylamino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or 4-(C₁₋₃-alkyl)-piperazin-1-yl group,

a formylamino, C₁₋₃-alkyl-carbonylamino, C₃₋₆-cycloalkyl-carbonylamino, C₃₋₆-cycloalkyl-C₁₋₃-alkyl-carbonylamino, arylcarbonylamino, aryl-C₁₋₃-alkyl-carbonylamino, C₁₋₃-alkyloxy-carbonylamino, aminocarbonylamino, C₁₋₃-alkyl-amino-carbonylamino, di-(C₁₋₃-alkyl)-aminocarbonylamino, pyrrolidin-1-yl-carbonylamino, 5 piperidin-1-yl-carbonylamino, morpholin-4-yl-carbonylamino, piperazin-1-yl-carbonylamino or 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonylamino, C₁₋₃-alkyl-sulphonylamino, bis-(C₁₋₃-alkylsulphonyl)-amino, aminosulphonylamino, C₁₋₃-alkyl-amino-sulphonylamino, di-(C₁₋₃-alkyl)-amino-sulphonylamino, pyrrolidin-1-yl-sulphonylamino, piperidin-1-yl-sulphonylamino, morpholin-4-yl-sulphonylamino, 10 piperazin-1-yl-sulphonylamino or 4-(C₁₋₃-alkyl)-piperazin-1-yl-sulphonylamino, (C₁₋₃-alkylamino)-thiocarbonylamino, (C₁₋₃-alkyloxy-carbonylamino)-carbonylamino, arylsulphonylamino or aryl-C₁₋₃-alkyl-sulphonylamino group,

an N-(C₁₋₃-alkyl)-formylamino, N-(C₁₋₃-alkyl)-N-(C₁₋₃-alkyl-carbonyl)-amino, N-(C₁₋₃-alkyl)-N-(C₃₋₆-cycloalkyl-carbonyl)-amino, N-(C₁₋₃-alkyl)-N-(C₃₋₆-cycloalkyl-C₁₋₃-alkyl-carbonyl)-amino, N-(C₁₋₃-alkyl)-N-(arylcarbonyl)-amino, N-(C₁₋₃-alkyl)-N-(aryl-C₁₋₃-alkyl-carbonyl)-amino, N-(C₁₋₃-alkyl)-N-(C₁₋₃-alkyloxy-carbonyl)-amino, N-(aminocarbonyl)-N-(C₁₋₃-alkyl)-amino, N-(C₁₋₃-alkyl-aminocarbonyl)-N-(C₁₋₃-alkyl)-amino, N-[di-(C₁₋₃-alkyl)aminocarbonyl]-N-(C₁₋₃-alkyl)-amino, N-(C₁₋₃-alkyl)-N-(C₁₋₃-alkyl-sulphonyl)-amino, N-(C₁₋₃-alkyl)-N-(arylsulphonyl)-amino or 20 N-(C₁₋₃-alkyl)-N-(aryl-C₁₋₃-alkyl-sulphonyl)-amino group,

a 2-oxo-imidazolidin-1-yl, 2,4-dioxo-imidazolidin-1-yl, 2,5-dioxo-imidazolidin-1-yl or 2-oxo-hexahydropyrimidin-1-yl group wherein the nitrogen atom in the 3 position 25 may be substituted in each case by a methyl or ethyl group,

a cyano, carboxy, C₁₋₃-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl or 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl group, 30

a C₁₋₃-alkyl-carbonyl or an arylcarbonyl group,

a carboxy-C₁₋₃-alkyl, C₁₋₃-alkyloxy-carbonyl-C₁₋₃-alkyl, cyano-C₁₋₃-alkyl,
aminocarbonyl-C₁₋₃-alkyl, C₁₋₃-alkyl-aminocarbonyl-C₁₋₃-alkyl, di-(C₁₋₃-alkyl)-
aminocarbonyl-C₁₋₃-alkyl, pyrrolidin-1-yl-carbonyl-C₁₋₃-alkyl, piperidin-1-yl-
carbonyl-C₁₋₃-alkyl, morpholin-4-yl-carbonyl-C₁₋₃-alkyl, piperazin-1-yl-carbonyl-C₁₋₃-
alkyl or 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl-C₁₋₃-alkyl group,

a carboxy-C₁₋₃-alkyloxy, C₁₋₃-alkyloxy-carbonyl-C₁₋₃-alkyloxy, cyano-C₁₋₃-alkyloxy,
aminocarbonyl-C₁₋₃-alkyloxy, C₁₋₃-alkyl-aminocarbonyl-C₁₋₃-alkyloxy, di-(C₁₋₃-
alkyl)-aminocarbonyl-C₁₋₃-alkyloxy, pyrrolidin-1-yl-carbonyl-C₁₋₃-alkyl-oxy,
piperidin-1-yl-carbonyl-C₁₋₃-alkyloxy, morpholin-4-yl-carbonyl-C₁₋₃-alkyl-oxy,
piperazin-1-yl-carbonyl-C₁₋₃-alkyloxy or 4-(C₁₋₃-alkyl)-piperazin-1-yl-carbonyl-C₁₋₃-
alkyloxy group,

a hydroxy-C₁₋₃-alkyl, C₁₋₃-alkyloxy-C₁₋₃-alkyl, amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-
alkyl, di-(C₁₋₃-alkyl)-amino-C₁₋₃-alkyl, pyrrolidin-1-yl-C₁₋₃-alkyl, piperidin-1-yl-C₁₋₃-
alkyl, morpholin-4-yl-C₁₋₃-alkyl, piperazin-1-yl-C₁₋₃-alkyl, 4-(C₁₋₃-alkyl)-piperazin-
1-yl-C₁₋₃-alkyl group,

a hydroxy-C₁₋₃-alkyloxy, C₁₋₃-alkyloxy-C₁₋₃-alkyloxy, C₁₋₃-alkylsulphanyl-C₁₋₃-
alkyloxy, C₁₋₃-alkylsulphanyl-C₁₋₃-alkyloxy, C₁₋₃-alkylsulphonyl-C₁₋₃-alkyloxy,
amino-C₁₋₃-alkyloxy, C₁₋₃-alkylamino-C₁₋₃-alkyloxy, di-(C₁₋₃-alkyl)-amino-C₁₋₃-
alkyloxy, pyrrolidin-1-yl-C₁₋₃-alkyloxy, piperidin-1-yl-C₁₋₃-alkyloxy, morpholin-4-
yl-C₁₋₃-alkyloxy, piperazin-1-yl-C₁₋₃-alkyloxy, 4-(C₁₋₃-alkyl)-piperazin-1-yl-C₁₋₃-
alkyloxy group,

a mercapto, C₁₋₃-alkylsulphanyl, C₁₋₃-alkylsulphanyl, C₁₋₃-alkylsulphonyl, C₁₋₃-
alkylsulphonyloxy, arylsulphonyloxy, trifluoromethylsulphanyl,
trifluoromethylsulphanyl or trifluoromethylsulphonyl group,

- a sulpho, aminosulphonyl, C₁₋₃-alkyl-aminosulphonyl, di-(C₁₋₃-alkyl)-amino-sulphonyl, pyrrolidin-1-yl-sulphonyl, piperidin-1-yl-sulphonyl, morpholin-4-yl-sulphonyl, piperazin-1-yl-sulphonyl or 4-(C₁₋₃-alkyl)-piperazin-1-yl-sulphonyl group,
- 5 a methyl or methoxy group substituted by 1 to 3 fluorine atoms,
- an ethyl or ethyloxy group substituted by 1 to 5 fluorine atoms,
- a C₂₋₄-alkenyl or C₂₋₄-alkynyl group,
- 10 a C₃₋₄-alkenyloxy or C₃₋₄-alkynyloxy group,
- a C₃₋₆-cycloalkyl or C₃₋₆-cycloalkyloxy group,
- 15 a C₃₋₆-cycloalkyl-C₁₋₃-alkyl or C₃₋₆-cycloalkyl-C₁₋₃-alkyloxy group or
- an aryl, aryloxy, aryl-C₁₋₃-alkyl or aryl-C₁₋₃-alkyloxy group,
- R¹¹ and R¹², which may be identical or different, in each case represent a hydrogen
- 20 atom, a fluorine, chlorine, bromine or iodine atom, a C₁₋₃-alkyl, trifluoromethyl, hydroxy, C₁₋₃-alkyloxy or cyano group, or
- R¹¹ together with R¹², if they are bound to adjacent carbon atoms, also represent a methylenedioxy, difluoromethylenedioxy or a straight-chain C₃₋₅-alkylene group and
- 25 R¹³ and R¹⁴, which may be identical or different, in each case represent a hydrogen atom, a fluorine, chlorine or bromine atom, a trifluoromethyl, C₁₋₃-alkyl or C₁₋₃-alkyloxy group,
- 30 a phenyl-C₁₋₄-alkyl group wherein the alkyl moiety is substituted by a cyano, carboxy, C₁₋₃-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkyl-aminocarbonyl, di-(C₁₋₃-alkyl)-

aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl-group and the phenyl moiety is substituted by the groups R^{10} to R^{14} , while R^{10} to R^{14} are as hereinbefore defined,

- 5 a phenyl group substituted by the groups R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

a phenyl- C_{2-3} -alkenyl group wherein the phenyl moiety is substituted by the groups R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

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a phenyl- $(CH_2)_m$ -A- $(CH_2)_n$ -group wherein the phenyl moiety is substituted by R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined and

- 15 A represents a carbonyl group, m represents the number 0, 1 or 2 and n represents the number 1, 2 or 3,

a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined and the methyl moiety is substituted by a C_{1-3} -alkyl group,

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a phenyl- $(CH_2)_m$ -B- $(CH_2)_n$ -group wherein the phenyl moiety is substituted by R^{10} to R^{14} , where R^{10} to R^{14} , m and n are as hereinbefore defined and

- 25 B denotes a methylene group which is substituted by a hydroxy, C_{1-3} -alkyloxy, amino, C_{1-3} -alkylamino, di- $(C_{1-3}$ -alkyl)-amino, mercapto, C_{1-3} -alkylsulphanyl, C_{1-3} -alkylsulphinyl or C_{1-3} -alkylsulphonyl group and is optionally additionally substituted by a methyl or ethyl group,

- 30 a naphthyl- C_{1-3} -alkyl group wherein the naphthyl moiety is substituted by the groups R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

- a naphthyl-(CH₂)_m-A-(CH₂)_n-group wherein the naphthyl moiety is substituted by R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴, A, m and n are as hereinbefore defined,
- a naphthyl-(CH₂)_m-B-(CH₂)_n-group wherein the naphthyl moiety is substituted by R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴, B, m and n are as hereinbefore defined,
- 5 a [1,4]naphthoquinon-2-yl, chromen-4-on-3-yl, 1-oxoindan-2-yl, 1,3-dioxoindan-2-yl or 2,3-dihydro-3-oxo-benzofuran-2-yl group,
- 10 a heteroaryl-(CH₂)_m-A-(CH₂)_n group where A, m and n are as hereinbefore defined,
- a heteroaryl-(CH₂)_m-B-(CH₂)_n group where B, m and n are as hereinbefore defined,
- a C₁₋₆-alkyl-A-(CH₂)_n group where A and n are as hereinbefore defined,
- 15 a C₃₋₇-cycloalkyl-(CH₂)_m-A-(CH₂)_n group where A, m and n are as hereinbefore defined,
- a C₃₋₇-cycloalkyl-(CH₂)_m-B-(CH₂)_n group where B, m and n are as hereinbefore defined,
- 20 an R²¹-A-(CH₂)_n-group wherein R²¹ denotes a C₁₋₃-alkyloxycarbonyl, aminocarbonyl, C₁₋₃-alkylaminocarbonyl, di-(C₁₋₃-alkyl)aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl or morpholin-4-yl-carbonyl, piperazin-1-yl-carbonyl, 4-methylpiperazin-1-yl-carbonyl or 4-ethylpiperazin-1-yl-carbonyl group and A and n are as hereinbefore defined,
- 25 a phenyl-(CH₂)_m-D-C₁₋₃-alkyl group wherein the phenyl moiety is substituted by the groups R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴ and m are as mentioned hereinbefore and D denotes an oxygen or sulphur atom, an imino, C₁₋₃-alkylimino, sulphinyl or sulphonyl group,
- 30 a naphthyl-(CH₂)_m-D-C₁₋₃-alkyl group wherein the naphthyl moiety is substituted by the groups R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴, D and m are as mentioned hereinbefore,

a C₂₋₆-alkyl group substituted by a group R_b, where

5 R_b is isolated from the cyclic nitrogen atom in the 1 position of the purine skeleton
by at least two carbon atoms and

R_b denotes a hydroxy, C₁₋₃-alkyloxy, mercapto, C₁₋₃-alkylsulphanyl, C₁₋₃-
alkylsulphinyl, C₁₋₃-alkylsulphonyl, amino, C₁₋₃-alkyl-carbonylamino, C₃₋₆-
cycloalkyl-carbonyl-amino, arylcarbonylamino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-
10 amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or 4-(C₁₋₃-
alkyl)-piperazin-1-yl group,

a C₃₋₆-cycloalkyl group,

15 or an amino or arylcarbonylamino group,

R² denotes a hydrogen atom,

a C₁₋₈-alkyl group,

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a C₃₋₈-alkenyl group,

a C₃₋₄-alkenyl group which is substituted by a C₁₋₂-alkyloxy-carbonyl, aminocarbonyl, C₁-
3-alkylamino-carbonyl, di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl,
25 piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

a C₃₋₈-alkynyl group,

a C₃₋₆-cycloalkyl group,

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a C₁₋₆-alkyl group substituted by a group R_a, where R_a is as hereinbefore defined,

a phenyl group which is substituted by R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

- 5 a C_{1-6} -alkyl group substituted by a phenyl group, wherein the phenyl ring is substituted by the groups R^{10} to R^{14} and R^{10} to R^{14} are as hereinbefore defined,

- a phenyl- C_{1-4} -alkyl group wherein the alkyl moiety is substituted by a cyano, carboxy, C_{1-3} -alkyloxy-carbonyl, aminocarbonyl, C_{1-3} -alkyl-aminocarbonyl, di- $(C_{1-3}$ -alkyl)-
10 aminocarbonyl, pyrrolidin-1-yl-carbonyl, piperidin-1-yl-carbonyl, morpholin-4-yl-carbonyl group and the phenyl moiety is substituted by the groups R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

- a phenyl- C_{2-3} -alkenyl group wherein the phenyl moiety is substituted by R^{10} to R^{14} , where
15 R^{10} to R^{14} are as hereinbefore defined,

a heteroaryl group,

- a phenyl- $(CH_2)_m$ -A or phenyl- $(CH_2)_m$ -A- $(CH_2)_n$ group wherein the phenyl moiety is
20 substituted in each case by R^{10} to R^{14} , while A, R^{10} to R^{14} , m and n are as hereinbefore defined,

- a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10} to R^{14} ,
where R^{10} to R^{14} are as hereinbefore defined and the methyl moiety is substituted by a C_{1-3} -alkyl group,
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- a phenyl- $(CH_2)_m$ -B or phenyl- $(CH_2)_m$ -B- $(CH_2)_n$ group wherein the phenyl moiety is
substituted in each case by R^{10} to R^{14} , while B, R^{10} to R^{14} , m and n are as hereinbefore
defined,

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a naphthyl- C_{1-3} -alkyl group wherein the naphthyl moiety is substituted by the groups R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

5 a naphthyl- $(CH_2)_m$ -A or naphthyl- $(CH_2)_m$ -A- $(CH_2)_n$ group wherein the naphthyl moiety is substituted in each case by R^{10} to R^{14} , where R^{10} to R^{14} , A, m and n are as hereinbefore defined,

10 a naphthyl- $(CH_2)_m$ -B or naphthyl- $(CH_2)_m$ -B- $(CH_2)_n$ group wherein the naphthyl moiety is substituted in each case by R^{10} to R^{14} , where R^{10} to R^{14} , B, m and n are as hereinbefore defined,

a heteroaryl- $(CH_2)_m$ -A or heteroaryl- $(CH_2)_m$ -A- $(CH_2)_n$ group where A, m and n are as hereinbefore defined,

15 a heteroaryl- $(CH_2)_m$ -B or heteroaryl- $(CH_2)_m$ -B- $(CH_2)_n$ group where B, m and n are as hereinbefore defined,

a C_{1-6} -alkyl-A or C_{1-6} -alkyl-A- $(CH_2)_n$ group where A and n are as hereinbefore defined,

20 a C_{3-7} -cycloalkyl- $(CH_2)_m$ -A or C_{3-7} -cycloalkyl- $(CH_2)_m$ -A- $(CH_2)_n$ group where A, m and n are as hereinbefore defined,

a C_{3-7} -cycloalkyl- $(CH_2)_m$ -B or C_{3-7} -cycloalkyl- $(CH_2)_m$ -B- $(CH_2)_n$ group where B, m and n are as hereinbefore defined,

25 an R^{21} -A- $(CH_2)_n$ group wherein R^{21} , A and n are as hereinbefore defined,

a phenyl- $(CH_2)_m$ -D- C_{1-3} -alkyl group wherein the phenyl moiety is substituted by the groups R^{10} to R^{14} , where R^{10} to R^{14} , D and m are as mentioned hereinbefore,

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a naphthyl-(CH₂)_m-D-C₁₋₃-alkyl group wherein the naphthyl moiety is substituted by the groups R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴, D and m are as mentioned hereinbefore,

a C₁₋₆-alkyl group substituted by a group R_b, where R_b is as hereinbefore defined,

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a cyano, carboxy, C₁₋₃-alkyloxy-carbonyl, aminocarbonyl, C₁₋₃-alkylamino-carbonyl, di-(C₁₋₃-alkyl)-amino-carbonyl, pyrrolidin-1-ylcarbonyl, piperidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, piperazin-1-ylcarbonyl, 4-methylpiperazin-1-ylcarbonyl or 4-ethylpiperazin-1-ylcarbonyl group,

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an amino, C₁₋₆-alkylamino or di-(C₁₋₆-alkyl)-amino group,

an amino group substituted by the groups R¹⁵ and R¹⁶ wherein

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R¹⁵ denotes a hydrogen atom or a C₁₋₆-alkyl group and

R¹⁶ denotes a C₁₋₆-alkyl group which is substituted by R_a, where R_a is as hereinbefore defined,

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an amino group substituted by the groups R¹⁵ and R¹⁷ wherein

R¹⁵ is as hereinbefore defined and

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R¹⁷ denotes a C₂₋₆-alkyl group which is substituted by a hydroxy, C₁₋₃-alkyloxy, aryloxy, mercapto, C₁₋₃-alkylsulphanyl, C₁₋₃-alkylsulphinyl, C₁₋₃-alkylsulphonyl, C₁₋₃-alkylsulphonylamino, arylsulphanyl, arylsulphinyl, arylsulphonyl, arylsulphonylamino, C₁₋₃-alkyl-carbonylamino, C₃₋₆-cycloalkyl-carbonylamino, arylcarbonylamino, C₁₋₃-alkyl-oxycarbonylamino, aminocarbonylamino, C₁₋₃-alkyl-aminocarbonylamino, di-(C₁₋₃-alkyl)-aminocarbonylamino, amino, C₁₋₃-alkylamino, di-(C₁₋₃-alkyl)-amino, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or 4-(C₁₋₃-alkyl)-piperazin-1-yl group,

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a C₃₋₆-cycloalkylamino or N-(C₃₋₆-cycloalkyl)-N-(C₁₋₃-alkyl)-amino group,

5 a phenylamino or N-(phenyl)-N-(C₁₋₃-alkyl)-amino group wherein the phenyl moiety is substituted in each case by R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴ are as hereinbefore defined,

a phenyl-C₁₋₆-alkylamino or N-(phenyl-C₁₋₆-alkyl)-N-(C₁₋₃-alkyl)-amino group wherein the phenyl moiety is substituted in each case by R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴ are as hereinbefore defined,

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a naphthylamino or N-(naphthyl)-N-(C₁₋₃-alkyl)-amino group,

a naphthyl-C₁₋₆-alkylamino or N-(naphthyl-C₁₋₆-alkyl)-N-(C₁₋₃-alkyl)-amino group,

15 a heteroaryl amino or N-(heteroaryl)-N-(C₁₋₃-alkyl)-amino group,

a pyrrolidin-1-yl, piperidin-1-yl, homopiperidin-1-yl, morpholin-4-yl, homomorpholin-4-yl, piperazin-1-yl, 4-(C₁₋₃-alkyl)-piperazin-1-yl, homopiperazin-1-yl or 4-(C₁₋₃-alkyl)-homopiperazin-1-yl group, or

20

a C₁₋₆-alkyloxy, C₃₋₆-cycloalkyloxy or C₃₋₆-cycloalkyl-C₁₋₆-alkyloxy group,

a C₁₋₆-alkylsulphanyl, C₃₋₆-cycloalkylsulphanyl or C₃₋₆-cycloalkyl-C₁₋₆-alkylsulphanyl group,

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a phenyloxy or phenylsulphanyl group wherein the phenyl moiety is substituted in each case by R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴ are as hereinbefore defined,

30 a phenyl-C₁₋₆-alkyloxy or phenyl-C₁₋₆-alkylsulphanyl group wherein the phenyl moiety is substituted in each case by R¹⁰ to R¹⁴, where R¹⁰ to R¹⁴ are as hereinbefore defined,

a naphthyloxy or a naphthylsulphanyl group wherein the naphthyl moiety is substituted in each case by R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

5 a naphthyl- C_{1-6} -alkyloxy or naphthyl- C_{1-6} -alkylsulphanyl group wherein the naphthyl moiety is substituted in each case by R^{10} to R^{14} , where R^{10} to R^{14} are as hereinbefore defined,

a heteroaryloxy or heteroarylsulphanyl group or

10 a heteroaryl- C_{1-6} -alkyloxy or heteroaryl- C_{1-6} -alkylsulphanyl group,

R^3 denotes a C_{1-8} -alkyl group,

a C_{1-4} -alkyl group substituted by the group R_c , where

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R_c denotes a C_{3-7} -cycloalkyl group optionally substituted by one or two C_{1-3} -alkyl groups,

a C_{5-7} -cycloalkenyl group optionally substituted by one or two C_{1-3} -alkyl groups,

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an aryl group or

a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidyl or pyrazinyl group, while the above-mentioned heterocyclic groups may
25 each be substituted by one or two C_{1-3} -alkyl groups or by a fluorine, chlorine, bromine or iodine atom or by a trifluoromethyl, cyano or C_{1-3} -alkyloxy group,

a C_{3-8} -alkenyl group,

30 a C_{3-6} -alkenyl group substituted by a fluorine, chlorine or bromine atom or a trifluoromethyl group,

a C₃₋₈-alkynyl group,

an aryl group or

5

an aryl-C₂₋₄-alkenyl group,

and

10 R⁴ denotes an azetidin-1-yl or pyrrolidin-1-yl group which is substituted in the 3 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group and may additionally be substituted by one or two C₁₋₃-alkyl groups,

15 a piperidin-1-yl or hexahydroazepin-1-yl group which is substituted in the 3 position or in the 4 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)amino group and may additionally be substituted by one or two C₁₋₃-alkyl groups,

20 a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl-moiety is additionally substituted by an aminocarbonyl, C₁₋₂-alkyl-aminocarbonyl, di-(C₁₋₂-alkyl)-aminocarbonyl, pyrrolidin-1-yl-carbonyl, (2-cyano-pyrrolidin-1-yl)-carbonyl, thiazolidin-3-yl-carbonyl, (4-cyano-thiazolidin-3-yl)carbonyl, piperidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

25 a 3-amino-piperidin-1-yl group wherein the piperidin-1-yl moiety is additionally substituted in the 4 position or 5 position by a hydroxy or methoxy group,

a 3-amino-piperidin-1-yl group wherein the methylene group is replaced in the 2 position or 6 position by a carbonyl group,

30 a piperidin-1-yl or hexahydroazepin-1-yl- group substituted in the 3 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, wherein two hydrogen atoms on the

carbon skeleton of the piperidin-1-yl or hexahydroazepin-1-yl group are each replaced by a straight-chain alkylene bridge, this bridge containing 2 to 5 carbon atoms if the two hydrogen atoms are on the same carbon atom, or 1 to 4 carbon atoms if the hydrogen atoms are on adjacent carbon atoms, or 1 to 4 carbon atoms if the hydrogen atoms are on carbon atoms which are separated by one atom, or 1 to 3 carbon atoms if the hydrogen atoms are on carbon atoms which are separated by two atoms,

an azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl or hexahydroazepin-1-yl group which is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

a piperazin-1-yl or [1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C₁₋₃-alkyl groups,

a 3-imino-piperazin-1-yl, 3-imino-[1,4]diazepan-1-yl or 5-imino-[1,4]diazepan-1-yl group optionally substituted on the carbon skeleton by one or two C₁₋₃-alkyl groups,

a [1,4]diazepan-1-yl group optionally substituted by one or two C₁₋₃-alkyl groups, which is substituted in the 6 position by an amino group,

a C₃₋₇-cycloalkyl group which is substituted by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

a C₃₋₇-cycloalkyl group which is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

a C₃₋₇-cycloalkyl-C₁₋₂-alkyl group wherein the cycloalkyl moiety is substituted by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

a C₃₋₇-cycloalkyl-C₁₋₂-alkyl group wherein the cycloalkyl moiety is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

a C₃₋₇-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

5

an N-(C₃₋₇-cycloalkyl)-N-(C₁₋₃-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group, while the two nitrogen atoms on the cycloalkyl moiety are separated from one another by at least two carbon atoms,

10

a C₃₋₇-cycloalkylamino group wherein the cycloalkyl moiety is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

15

an N-(C₃₋₇-cycloalkyl)-N-(C₁₋₃-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

20

a C₃₋₇-cycloalkyl-C₁₋₂-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

an N-(C₃₋₇-cycloalkyl-C₁₋₂-alkyl)-N-(C₁₋₂-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

25 a C₃₋₇-cycloalkyl-C₁₋₂-alkyl-amino group wherein the cycloalkyl moiety is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

30 an N-(C₃₋₇-cycloalkyl-C₁₋₂-alkyl)-N-(C₁₋₂-alkyl)-amino group wherein the cycloalkyl moiety is substituted by an amino-C₁₋₃-alkyl, C₁₋₃-alkylamino-C₁₋₃-alkyl or a di-(C₁₋₃-alkyl)amino-C₁₋₃-alkyl group,

an R¹⁹-C₂₋₄-alkylamino group wherein R¹⁹ is separated from the nitrogen atom of the C₂₋₄-alkylamino moiety by at least two carbon atoms and

R¹⁹ denotes an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)-amino group,

5

an R¹⁹-C₂₋₄-alkylamino group wherein the nitrogen atom of the C₂₋₄-alkylamino moiety is substituted by a C₁₋₃-alkyl group and R¹⁹ is separated from the nitrogen atom of the C₂₋₄-alkylamino moiety by at least two carbon atoms, where R¹⁹ is as hereinbefore defined,

10 an amino group substituted by the group R²⁰ wherein

R²⁰ denotes an azetidin-3-yl, azetidin-2-ylmethyl, azetidin-3-ylmethyl, pyrrolidin-3-yl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, piperidin-3-yl, piperidin-4-yl, piperidin-2-ylmethyl, piperidin-3-ylmethyl or piperidin-4-ylmethyl group, while the
15 groups mentioned for R²⁰ may each be substituted by one or two C₁₋₃-alkyl groups,

an amino group substituted by the group R²⁰ and a C₁₋₃-alkyl group wherein R²⁰ is as hereinbefore defined, while the groups mentioned for R²⁰ may each be substituted by one or two C₁₋₃-alkyl groups,

20

an R¹⁹-C₃₋₄-alkyl group wherein the C₃₋₄-alkyl moiety is straight-chained and may additionally be substituted by one or two C₁₋₃-alkyl groups, where R¹⁹ is as hereinbefore defined,

25 a 3-amino-2-oxo-piperidin-5-yl or 3-amino-2-oxo-1-methyl-piperidin-5-yl group,

a pyrrolidin-3-yl, piperidin-3-yl, piperidin-4-yl, hexahydroazepin-3-yl or hexahydroazepin-4-yl group which is substituted in the 1 position by an amino, C₁₋₃-alkylamino or di-(C₁₋₃-alkyl)amino group,

30

or an azetidin-2-yl-C₁₋₂-alkyl, azetidin-3-yl-C₁₋₂-alkyl, pyrrolidin-2-yl-C₁₋₂-alkyl, pyrrolidin-3-yl, pyrrolidin-3-yl-C₁₋₂-alkyl, piperidin-2-yl-C₁₋₂-alkyl, piperidin-3-yl, piperidin-3-yl-C₁₋₂-alkyl, piperidin-4-yl or piperidin-4-yl-C₁₋₂-alkyl group, while the above-mentioned groups may each be substituted by one or two C₁₋₃-alkyl groups,

5

while by the aryl groups mentioned in the definition of the above groups are meant phenyl or naphthyl groups, which may be mono- or disubstituted by R_h independently of one another, where the substituents are identical or different and R_h denotes a fluorine, chlorine, bromine or iodine atom, a trifluoromethyl, cyano, nitro, amino, aminocarbonyl, aminosulphonyl, methylsulphonyl, acetylamino, methylsulphonylamino, C₁₋₃-alkyl, cyclopropyl, ethenyl, ethynyl, hydroxy, C₁₋₃-alkyloxy, difluoromethoxy or trifluoromethoxy group,

10

by the heteroaryl groups mentioned in the definitions of the above-mentioned groups are meant a pyrrolyl, furanyl, thienyl, pyridyl, indolyl, benzofuranyl, benzothiophenyl, quinolinylyl or isoquinolinylyl group,

15

or a pyrrolyl, furanyl, thienyl or pyridyl group wherein one or two methyne groups are replaced by nitrogen atoms,

20

or an indolyl, benzofuranyl, benzothiophenyl, quinolinylyl or isoquinolinylyl group wherein one to three methyne groups are replaced by nitrogen atoms,

25

or a 1,2-dihydro-2-oxo-pyridinyl, 1,4-dihydro-4-oxo-pyridinyl, 2,3-dihydro-3-oxo-pyridazinyl, 1,2,3,6-tetrahydro-3,6-dioxo-pyridazinyl, 1,2-dihydro-2-oxo-pyrimidinyl, 3,4-dihydro-4-oxo-pyrimidinyl, 1,2,3,4-tetrahydro-2,4-dioxo-pyrimidinyl, 1,2-dihydro-2-oxo-pyrazinyl, 1,2,3,4-tetrahydro-2,3-dioxo-pyrazinyl, 2,3-dihydro-2-oxo-indolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydro-2-oxo-1H-benzimidazolyl, 2,3-dihydro-2-oxo-benzoxazolyl, 1,2-dihydro-2-oxo-quinolinylyl, 1,4-dihydro-4-oxo-quinolinylyl, 1,2-dihydro-1-oxo-isoquinolinylyl, 1,4-dihydro-4-oxo-cinnolinylyl, 1,2-dihydro-2-oxo-quinazolinylyl, 3,4-dihydro-4-oxo-quinazolinylyl, 1,2,3,4-tetrahydro-2,4-dioxo-quinazolinylyl, 1,2-dihydro-2-

30

oxoquinoxaliny, 1,2,3,4-tetrahydro-2,3-dioxo-quinoxaliny, 1,2-dihydro-1-oxo-phthalaziny, 1,2,3,4-tetrahydro-1,4-dioxo-phthalaziny, chromanyl, cumariny, 2,3-dihydro-benzo[1,4]dioxiny or 3,4-dihydro-3-oxo-2H-benzo[1,4]oxaziny group,

5 while the above-mentioned heteroaryl groups may be substituted by R^{10} to R^{14} ,
where R^{10} to R^{14} are as hereinbefore defined,

and, unless otherwise stated, the above-mentioned alkyl, alkenyl and alkynyl groups may be straight-chain or branched,

10

as well as the derivatives which are N-oxidised or methylated or ethylated at the cyclic nitrogen atom in the 3 position or 9 position of the hypoxanthine skeleton,

as well as the derivatives wherein the 6-oxo group of the hypoxanthine skeleton is
15 replaced by a thioxo group,

with the proviso that the compounds

8-(piperidin-4-ylmethyl)-7-(4-fluorobenzyl)-1,7-dihydro-purin-6-one and
20

8-(1-methyl-piperidin-4-ylmethyl)-7-(4-fluorobenzyl)-1,7-dihydro-purin-6-one

are excluded,

25 the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs thereof and the salts thereof.

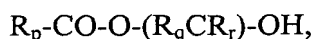
Compounds which contain a group that can be cleaved in vivo are prodrugs of the corresponding compounds wherein this group that can be cleaved in vivo has been
30 cleaved.

The carboxy groups mentioned in the definition of the above-mentioned groups may be replaced by a group which can be converted into a carboxy group in vivo or by a group which is negatively charged under physiological conditions,

5 and furthermore the amino and imino groups mentioned in the definition of the above-mentioned groups may be substituted by a group which can be cleaved in vivo. Such groups are described for example in WO 98/46576 and by N.M. Nielsen et al. in International Journal of Pharmaceutics 39, 75-85 (1987).

10 By a group which can be converted in vivo into a carboxy group is meant, for example, a hydroxymethyl group, a carboxy group esterified with an alcohol wherein the alcohol moiety is preferably a C₁₋₆-alkanol, a phenyl-C₁₋₃-alkanol, a C₃₋₉-cycloalkanol, while a C₅₋₈-cycloalkanol may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₅₋₈-cycloalkanol wherein a methylene group in the 3 or 4 position is replaced by an
15 oxygen atom or by an imino group optionally substituted by a C₁₋₃-alkyl, phenyl-C₁₋₃-alkyl, phenyl-C₁₋₃-alkyloxycarbonyl or C₂₋₆-alkanoyl group and the cycloalkanol moiety may additionally be substituted by one or two C₁₋₃-alkyl groups, a C₄₋₇-cycloalkenol, a C₃₋₅-alkenol, a phenyl-C₃₋₅-alkenol, a C₃₋₅-alkynol or phenyl-C₃₋₅-alkynol with the proviso that no bonds to the oxygen atom start from a carbon atom
20 which carries a double or triple bond, a C₃₋₈-cycloalkyl-C₁₋₃-alkanol, a bicycloalkanol with a total of 8 to 10 carbon atoms which may additionally be substituted in the bicycloalkyl moiety by one or two C₁₋₃-alkyl groups, a 1,3-dihydro-3-oxo-1-isobenzofuranol or an alcohol of formula

25



wherein

30 R_p denotes a C₁₋₈-alkyl, C₅₋₇-cycloalkyl, C₁₋₈-alkyloxy, C₅₋₇-cycloalkyloxy, phenyl or phenyl-C₁₋₃-alkyl group,

R_q denotes a hydrogen atom, a C_{1-3} -alkyl, C_{5-7} -cycloalkyl or phenyl group and

R_r denotes a hydrogen atom or a C_{1-3} -alkyl group,

5 by a group which is negatively charged under physiological conditions is meant, for example, a tetrazol-5-yl, phenylcarbonylaminocarbonyl, trifluoromethylcarbonylaminocarbonyl, C_{1-6} -alkylsulphonylamino, phenylsulphonylamino, benzylsulphonylamino, trifluoromethylsulphonylamino, C_{1-6} -alkylsulphonylaminocarbonyl, phenylsulphonylaminocarbonyl, 10 benzylsulphonylaminocarbonyl or perfluoro- C_{1-6} -alkylsulphonylaminocarbonyl group

and by a group which can be cleaved in vivo from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as a phenylcarbonyl group optionally mono- or disubstituted by fluorine, chlorine, bromine or iodine atoms, by C_{1-3} -alkyl or 15 C_{1-3} -alkyloxy groups, while the substituents may be identical or different, a pyridinoyl group or a C_{1-16} -alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, a 3,3,3-trichloropropionyl or allyloxycarbonyl group, a C_{1-16} -alkyloxycarbonyl or C_{1-16} -alkylcarbonyloxy group, wherein hydrogen atoms may be wholly or partially replaced by fluorine or chlorine atoms such as the methoxycarbonyl, 20 ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl, hexadecyloxycarbonyl, methylcarbonyloxy, ethylcarbonyloxy, 2,2,2-trichloro-ethylcarbonyloxy, propylcarbonyloxy, isopropylcarbonyloxy, butylcarbonyloxy, 25 tert.butylcarbonyloxy, pentylcarbonyloxy, hexylcarbonyloxy, octylcarbonyloxy, nonylcarbonyloxy, decylcarbonyloxy, undecylcarbonyloxy, dodecylcarbonyloxy or hexadecylcarbonyloxy group, a phenyl- C_{1-6} -alkyloxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a 3-amino-propionyl group wherein the amino group may be mono- or disubstituted by C_{1-6} -alkyl or 30 C_{3-7} -cycloalkyl groups and the substituents may be identical or different, a C_{1-3} -alkylsulphonyl- C_{2-4} -alkyloxycarbonyl, C_{1-3} -alkyloxy- C_{2-4} -alkyloxy-

C₂₋₄-alkyloxycarbonyl, R_p-CO-O-(R_qCR_r)-O-CO, C₁₋₆-alkyl-CO-NH-(R_sCR_t)-O-CO- or C₁₋₆-alkyl-CO-O-(R_sCR_t)-(R_sCR_t)-O-CO- group, wherein R_p to R_r are as hereinbefore defined,

5 R_s and R_t, which may be identical or different, denote hydrogen atoms or C₁₋₃-alkyl groups.

Moreover, the saturated alkyl and alkyloxy moieties which contain more than 2 carbon atoms mentioned in the foregoing definitions and those that follow, unless otherwise
10 stated, also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl, isobutyl group, etc.

One sub-group deserving special mention relates to those compounds of general formula
15 I wherein R¹, R² and R³ are as hereinbefore defined and

R⁴ denotes a pyrrolidin-1-yl group which is substituted in the 3 position by an amino group,

20 a piperidin-1-yl group which is substituted in the 3 position by an amino group,

a piperidin-3-yl or piperidin-4-yl group,

a hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an
25 amino group,

a piperazin-1-yl or [1,4]diazepan-1-yl group,

a (2-aminocyclohexyl)amino group,

30 a cyclohexyl group which is substituted in the 3 position by an amino group,

or an N-(2-aminoethyl)-methylamino or an N-(2-aminoethyl)-ethylamino group,

the tautomers, enantiomers, diastereomers, the mixtures thereof, the prodrugs and the
5 salts thereof.

Preferred compounds of the above general formula I are those wherein

10 R^1 denotes a hydrogen atom,

a C_{1-6} -alkyl group,

a C_{3-6} -alkenyl group,

15 a C_{3-4} -alkynyl group,

a C_{3-6} -cycloalkylmethyl group,

20 a phenyl- C_{1-3} -alkyl group wherein the phenyl moiety is substituted by R^{10} and R^{11} , where

R^{10} denotes a hydrogen atom, a fluorine, chlorine or bromine atom,

a methyl or trifluoromethyl group,

25 a cyano, aminocarbonyl, dimethylaminocarbonyl or methylsulphonyl group,

an amino, acetylamino or methylsulphonylamino group,

a hydroxy, methoxy, difluoromethoxy, trifluoromethoxy,

carboxymethoxy, methoxycarbonylmethoxy, ethyloxycarbonylmethoxy, aminocarbonylmethoxy, methylaminocarbonylmethoxy, ethylamino-carbonylmethoxy or dimethylaminocarbonylmethoxy group and

5 R^{11} denotes a hydrogen atom, a fluorine or chlorine atom,

or a methyl or methoxy group,

a naphthylmethyl group wherein the naphthyl moiety is substituted by R^{10} and R^{11} , where
10 R^{10} and R^{11} are as hereinbefore defined,

a heteroarylmethyl group where the term

heteroaryl denotes a furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl,
15 pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl or quinazolinyl group and the
above-mentioned heteroaryl groups are substituted by R^{10} and R^{11} , where R^{10} and
 R^{11} are as hereinbefore defined,

a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R^{10} and R^{11} ,
20 where R^{10} and R^{11} are as hereinbefore defined,

a furanylcabonylmethyl, thienylcarbonylmethyl or pyridylcarbonylmethyl group,

or a 2-oxo-propyl or cyclohexylcarbonylmethyl group,

25 R^2 denotes a hydrogen atom,

a C_{1-6} -alkyl group,

30 a C_{3-6} -alkenyl group,

a C₃₋₄-alkynyl group,

a C₃₋₆-cycloalkyl or C₃₋₆-cycloalkyl-C₁₋₃-alkyl group,

5 a phenyl group which is substituted by R¹⁰ and R¹¹, where R¹⁰ and R¹¹ are as hereinbefore defined,

a phenyl-C₁₋₃-alkyl group wherein the phenyl moiety is substituted by R¹⁰ and R¹¹, where R¹⁰ and R¹¹ are as hereinbefore defined,

10

a phenyl-C₂₋₃-alkenyl group wherein the phenyl moiety is substituted by R¹⁰ and R¹¹, where R¹⁰ and R¹¹ are as hereinbefore defined,

15 a phenylcarbonylmethyl group wherein the phenyl moiety is substituted by R¹⁰ and R¹¹, where R¹⁰ and R¹¹ are as hereinbefore defined,

a furanyl, thienyl or pyridyl group,

20 a furanyl-C₁₋₃-alkyl, thienyl-C₁₋₃-alkyl or pyridyl-C₁₋₃-alkyl group,

20

a cyano group,

an amino, C₁₋₄-alkylamino or di-(C₁₋₄-alkyl)-amino group,

25 an amino group substituted by the groups R¹⁵ and R¹⁶ wherein

R¹⁵ denotes a hydrogen atom or a methyl or ethyl group and

30 R¹⁶ denotes a C₁₋₄-alkyl group which is substituted by a cyano, carboxy, methoxycarbonyl, ethyloxycarbonyl, aminocarbonyl, methylaminocarbonyl,

dimethylaminocarbonyl, ethylaminocarbonyl, diethylaminocarbonyl, pyrrolidin-1-ylcarbonyl or morpholin-4-ylcarbonyl group,

an amino group substituted by the groups R¹⁵ and R¹⁷ wherein

5

R¹⁵ is as hereinbefore defined and

R¹⁷ denotes a straight-chain C₂₋₄-alkyl group which is terminally substituted in each case by an amino, methylamino, dimethylamino, acetylamino, ethyloxy-carbonylamino, phenylcarbonylamino, methylsulphonylamino,
10 phenylsulphonylamino, hydroxy, methoxy, phenyloxy, methylsulphanyl or phenylsulphanyl group,

a pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, piperazin-1-yl or 4-methyl-piperazin-1-yl group,
15

a C₃₋₆-cycloalkylamino or C₃₋₆-cycloalkyl-C₁₋₃-alkylamino group,

a phenylamino group,

20

a phenyl-C₁₋₃-alkylamino group wherein the phenyl moiety is substituted by R¹⁰ and R¹¹, where R¹⁰ and R¹¹ are as hereinbefore defined,

a naphthylmethylamino group,

25

a heteroaryl-C₁₋₂-alkylamino group, where the term heteroaryl is as hereinbefore defined, or

a methylsulphanyl, benzylsulphanyl or (2-phenylethyl)sulphanyl group,

30

R³ denotes a C₄₋₆-alkenyl group,

a C₃₋₄-alkenyl group which is substituted by a fluorine, chlorine or bromine atom or a trifluoromethyl group,

5 a 2-butyne-1-yl group or

a methyl group substituted by the group R_c, where

10 R_c denotes a 1-cyclopenten-1-yl or 1-cyclohexen-1-yl group,

a phenyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, by a methyl, trifluoromethyl, cyano, methoxy, difluoromethoxy or trifluoromethoxy group,

15 a phenyl group which is substituted by two fluorine atoms,

a naphthyl group or

a furanyl, thienyl, or pyridyl group,

20

and

R⁴ denotes a piperidin-1-yl group which is substituted in the 3 position by an amino group,

25

a hexahydroazepin-1-yl group which is substituted in the 3 position or 4 position by an amino group,

a (2-aminocyclohexyl)amino group,

30

a cyclohexyl group which is substituted in the 3 position by an amino group, or

an N-(2-aminoethyl)-methyldamino or an N-(2-aminoethyl)-ethylamino group,

while unless otherwise stated, the above-mentioned alkyl, alkenyl and alkynyl groups
5 may be straight-chain or branched,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein
10

R^1 denotes a hydrogen atom,

a methyl, benzyl or 2-phenylethyl group,

15 a naphthylmethyl or methoxynaphthylmethyl group or

a phenylcarbonylmethyl group,

R^2 denotes a hydrogen atom,
20

a methyl or 2-phenylethyl group,

a phenylcarbonylmethyl group,

25 a cyano group,

an amino, methylamino, dimethylamino, isopropylamino, cyclohexylamino-
or (cyclohexylmethyl)amino group,

30 a benzylamino, fluorobenzylamino or (2-phenylethyl)amino group or

a piperidin-1-yl group,

R^3 denotes a benzyl or 3-methyl-but-2-en-1-yl group

5 and

R^4 denotes a (3-amino-piperidin-1-yl) group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof,
10 but particularly the compounds

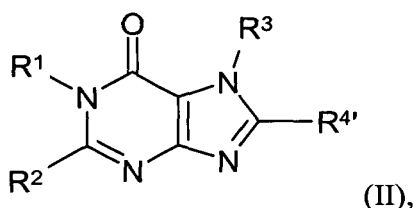
- (1) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-benzylamino-1-methyl-1,7-dihydro-purin-
6-one,
15
- (2) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-(4-fluoro-benzylamino)-1-methyl-1,7-
dihydro-purin-6-one,
- (3) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-phenylethyl)amino]-1,7-
20 dihydro-purin-6-one,
- (4) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-isopropylamino-1-methyl-1,7-dihydro-
purin-6-one,
- 25 (5) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-methylamino-1,7-dihydro-purin-
6-one,
- (6) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-cyclohexylamino-1-methyl-1,7-dihydro-
purin-6-one,
30

- (7) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-[(cyclohexylmethyl)amino]-1-methyl-1,7-dihydro-purin-6-one,
- (8) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(piperidin-1-yl)-1,7-dihydro-purin-6-one,
- (9) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-dimethylamino-1-methyl-1,7-dihydro-purin-6-one,
- (10) 2-amino-8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-1,7-dihydro-purin-6-one,
- (11) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-methyl-but-2-en-1-yl)-1,7-dihydro-purin-6-one,
- (12) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-methyl-1,7-dihydro-purin-6-one,
- (13) 8-(3-amino-piperidin-1-yl)-1-methyl-7-(3-methyl-but-2-en-1-yl)-2-(2-phenyl-ethyl)-1,7-dihydro-purin-6-one,
- (14) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-1,7-dihydro-purin-6-one,
- (15) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-oxo-2-phenyl-ethyl)-1,7-dihydro-purin-6-one,
- (16) 8-(3-amino-piperidin-1-yl)-2-methyl-7-(3-methyl-but-2-en-1-yl)-1-[(naphthalen-1-yl)methyl]-1,7-dihydro-purin-6-one,
- (17) 8-(3-amino-piperidin-1-yl)-7-(3-methyl-but-2-en-1-yl)-1-[(naphthalen-1-yl)methyl]-1,7-dihydro-purin-6-one and

(18) 8-(3-amino-piperidin-1-yl)-7-(3-methyl-but-2-en-1-yl)-1-[(4-methoxy-naphthalen-1-yl)methyl]-1,7-dihydro-purin-6-one

as well as the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

The compounds of general formula I can be prepared by deprotecting a compound of general formula



wherein R^1 , R^2 and R^3 are as hereinbefore defined and $R^{4'}$ denotes one of the groups mentioned hereinbefore for R^4 which contain an imino, amino or alkylamino group, while the imino, amino or alkylamino group is substituted by a protective group, optionally followed by subsequent alkylation of the imino, amino or C_{1-3} -alkylamino group.

The liberating of an amino group from a protected precursor is a standard reaction in synthetic organic chemistry. There are many examples of suitable protective groups. A summary of the chemistry of protective groups can be found in Theodora W. Greene and Peter G.M. Wuts, *Protective Groups in Organic Synthesis*, Second Edition, 1991, published by John Wiley and Sons, and in Philip J. Kocienski, *Protecting Groups*, published by Georg Thieme, 1994.

The following are examples of protective groups:

the tert.-butoxycarbonyl group which can be cleaved by treating with an acid such as for example trifluoroacetic acid or hydrogen chloride in the presence of a solvent such as for example methylene chloride, ethyl acetate or dioxane at temperatures between 0°C and the boiling temperature of the solvent used,

5

the 2,2,2-trichloroethoxycarbonyl group which can be cleaved by treating with metals such as for example zinc or cadmium in a solvent such as acetic acid or a mixture of tetrahydrofuran and a weak aqueous acid at temperatures between 0°C and the boiling temperature of the solvent used and

10

the carbobenzyloxycarbonyl group which can be cleaved for example by hydrogenolysis in the presence of a noble metal catalyst such as for example palladium-charcoal and a solvent such as for example alcohols, ethyl acetate, dioxane, tetrahydrofuran or mixtures of these solvents at temperatures between 0°C and the boiling point of the solvent, by treating with boron tribromide in methylene chloride at temperatures between -20°C and ambient temperature, or by treating with aluminium chloride/anisol at temperatures between 0°C and ambient temperature.

15

20

The optional subsequent introduction of a C₁₋₃-alkyl group may be done by alkylation or reductive alkylation.

25

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethyl sulphate, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

30

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde or acetone in the

presence of a complex metal hydride such as sodium borohydride, lithium borohydride, sodium triacetoxyborohydride or sodium cyanoborohydride, conveniently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of palladium/charcoal, under a hydrogen pressure of 1 to 5 bar.

- 5 The methylation may also be carried out in the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

The compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers. Thus, for example, cis/trans mixtures may be resolved into their cis
10 and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as
15 racemates may be separated by methods known per se (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known per se, e.g. by chromatography and/or fractional
20 crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active
25 substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active
30 acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolytartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid,

aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

- 5 Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methane sulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

10

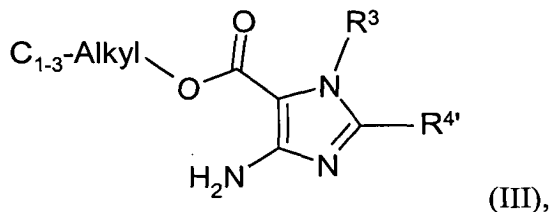
Moreover, if the new compounds of formula I thus obtained contain a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

15

The starting compounds of general formula II may be prepared by generally known methods and according to processes described for example in Examples I to XIV.

20

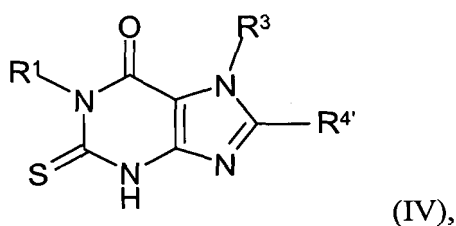
Thus, compounds of general formula II wherein R^1 , R^3 and $R^{4'}$ are as hereinbefore defined and R^2 denotes a hydrogen atom, may be prepared for example by reacting a compound of formula



25

with a formimido-C₁₋₃-alkyl ester, optionally followed by alkylation at N-1 with a suitable alkylating agent.

Compounds of general formula II wherein R¹, R³ and R^{4'} are as hereinbefore defined and
5 R² denotes an alkylsulphanyl, an alkenylsulphanyl or alkynylsulphanyl group may be obtained for example by reacting compounds of general formula III with a suitable isothiocyanate and subsequently cyclising them to form compounds of general formula



10 followed by alkylation of the sulphur atom.

If an acyl mustard oil is used, such as for example ethoxycarbonylisothiocyanate, first of all compounds of general formula IV, wherein R¹ denotes a hydrogen atom are obtained,
15 which can be converted into the desired compounds by subsequent alkylation at the sulphur atom and at N-1.

Compounds of general formula II wherein R¹, R³ and R^{4'} are as hereinbefore defined and
R² denotes an alkylsulphanyl group can be oxidised to form compounds of formula II'
20 wherein R^{2'} denotes an alkylsulphinyl or an alkylsulphonyl group.

The above-mentioned compounds of general formula II' are starting materials for preparing the following compounds of formula II.

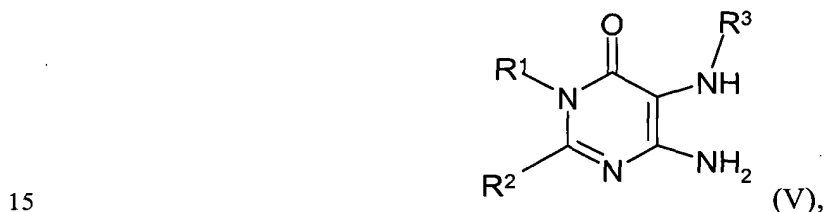
25 Reaction with alcohols and phenols yields compounds wherein the group R² is linked to the purine system via an oxygen atom,

Reaction with thiols and thiophenols leads to compounds wherein R^2 is linked to the purine system via a sulphur atom,

Reaction with amines leads to compounds wherein R^2 is bound to the purine system via a
5 nitrogen atom and

Reaction with organometallic compounds such as for example Grignard reagents, alkyl-
or aryl-lithium compounds or reaction with CH-acid compounds such as for example
esters, nitriles or ketones leads to compounds wherein R^2 is linked to the purine system
10 via a carbon atom.

Another method of obtaining compounds of general formula II consists, for example, in
converting compounds of general formula



wherein R^1 , R^2 and R^3 are as hereinbefore defined, into compounds of general formula II.

For example, compounds of general formula V are converted into compounds of general
20 formula II wherein the group $R^{4'}$ is bound to the purine system via a nitrogen atom, by
reacting with an orthoformate, subsequently brominating the resulting purine at C-8 and
then reacting with a corresponding amine.

For example, compounds of general formula V are converted into compounds of general
25 formula II wherein the group $R^{4'}$ is bound to the C-8 atom of the purine via a C-atom by
reaction with a reactive derivative of a carboxylic acid $R^{4'}-\text{COOH}$, where $R^{4'}$ is as
hereinbefore defined, and subsequent cyclisation.

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV.

5

The biological properties of the new compounds were investigated as follows:

The ability of the substances and their corresponding salts to inhibit the DPP-IV activity can be demonstrated in a test set-up in which an extract of human colon carcinoma cell
10 line Caco-2 is used as the DPP IV source. The differentiation of the cells in order to induce the DPP-IV expression was carried out as described by Reiher et al. in an article entitled "Increased expression of intestinal cell line Caco-2" , which appeared in Proc. Natl. Acad. Sci. Vol. 90, pages 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5%
15 Nonidet-P40, pH 8.0) by centrifuging at 35,000 g for 30 minutes at 4°C (to remove cell debris).

The DPP-IV assay was carried out as follows:

20 50 µl substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) was pipetted in. The reaction was started by adding 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances to be investigated were typically added
25 prediluted in 20 µl, and the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, incubating for 60 minutes. Then the fluorescence was measured in a Victor 1420 Multilabel Counter, the excitation wavelength being 405 nm and the emission wavelength being 535 nm. Blank readings (corresponding to 0 % activity) were obtained in mixtures without any Caco-2 protein
30 (volume replaced by assay buffer), control values (corresponding to 100 % activity) were obtained in mixtures with no substance added. The potency of the test substances in

question, expressed as IC_{50} values, was calculated from dosage/activity curves consisting of 11 measuring points in each case.

The results obtained are shown in the following Table:

5

Compound (Example No.)	DPP IV inhibition IC_{50} (nM)
1	11
1(1)	24
1(2)	42
1(3)	110
1(4)	58
1(5)	134
1(6)	48
1(7)	434
1(8)	213
1(9)	61
1(11)	54
1(12)	18
1(13)	152
1(14)	158
1(15)	58
1(22)	48
1(23)	157
1(24)	113
1(25)	275
1(26)	40
1(27)	19
1(28)	57

The compounds prepared according to the invention are well tolerated, as for example when 30 mg/kg of the compound of Example 1 were administered to rats by oral route no toxic side effects or changes in the animals' behaviour could be detected.

5 In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for treating all those conditions or illnesses which can be influenced by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or
10 conditions such as type 1 and type 2 diabetes mellitus, diabetic complications (such as e.g. retinopathy, nephropathy or neuropathies), metabolic acidosis or ketosis, reactive hypoglycaemia, insulin resistance, metabolic syndrome, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and calcitonin-induced osteoporosis. In addition these substances are capable of
15 preventing B-cell degeneration such as e.g. apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and also increasing the number and size of pancreatic B-cells. Additionally, and on the basis of the role of the Glucagon-Like Peptides, such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is likely that the compounds according to the
20 invention are suitable for achieving, inter alia, a sedative or anxiety-relieving effect and also of favourably affecting catabolic states after operations or hormonal stress responses or of reducing mortality or morbidity after myocardial infarct. They are also suitable for treating all conditions which are connected with the above-mentioned effects and which are mediated by GLP-1 or GLP-2. The compounds according to the invention may also
25 be used as diuretics or antihypertensives and are suitable for preventing and treating acute renal failure. Furthermore, the compounds according to the invention may be used to treat inflammatory diseases of the respiratory tract. They are also suitable for the prevention and treatment of chronic inflammatory intestinal diseases such as e.g. irritable bowel syndrome (IBS), Crohn's disease or ulcerative colitis and also pancreatitis. It is also likely
30 that they can be used for all kinds of damage to or impairment of the gastrointestinal tract such as colitis and enteritis, for example. It is also expected that DPP-IV inhibitors and

hence also the compounds according to the invention may be used to treat infertility or to improve fertility in humans or mammals, particularly when the infertility is connected with insulin resistance or polycystic ovary syndrome. On the other hand these substances are suitable for affecting sperm motility and can thus be used as male contraceptives. The substances are also suitable for treating deficiencies of growth hormone which are associated with reduced stature, and may also be used to advantage in any indications in which growth hormone may be used. The compounds according to the invention are also suitable, on the basis of their inhibitory effect on DPP IV, for treating various autoimmune diseases such as e.g. rheumatoid arthritis, multiple sclerosis, thyroiditis and Basedow's disease, etc. They may also be used to treat viral diseases and also, for example, in HIV infections, for stimulating blood production, in benign prostatic hyperplasia, gingivitis, as well as for the treatment of neuronal defects and neurodegenerative diseases such as Alzheimer's disease, for example. The compounds described may also be used for the treatment of tumours, particularly for modifying tumour invasion and also metastatisation; examples here are their use in treating T-cell lymphomas, acute lymphoblastic leukaemia, cell-based pancreatic carcinomas, basal cell carcinomas or breast cancers. Other indications are stroke, ischaemia of various origins, Parkinson's disease and migraine. In addition, further indications include follicular and epidermal hyperkeratoses, increased keratinocyte proliferation, psoriasis, encephalomyelitis, glomerulonephritis, lipodystrophies, as well as psychosomatic, depressive and neuropsychiatric diseases of all kinds.

The compounds according to the invention may also be used in conjunction with other active substances. Therapeutic agents which are suitable for such combinations include, for example, antidiabetics, such as metformin, sulphonylureas (e.g. glibenclamid, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinedione (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), alpha-glucosidase inhibitors (e.g. acarbose, voglibose), other DPPIV inhibitors, alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. Also, inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the

liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol - pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin),
5 fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. avasimibe) or cholesterol - resorption inhibitors such as for example ezetimibe, bile acid-binding substances such as for example cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or active
10 substances for the treatment of obesity such as e.g. sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or β_3 -agonists such as SB-418790 or AD-9677 as well as agonists of the 5HT2c receptor.

15 It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. AII antagonists or ACE inhibitors, diuretics, β -blockers, Ca-antagonists, etc., or combinations thereof.

The dosage required to achieve such an effect is expediently, by intravenous route, 1 to
20 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate,
25 polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

30

The Examples that follow are intended to illustrate the invention:

Preparation of the starting compounds:

5 Example I

Ethyl 5-amino-3-benzyl-2-(3-tert.-butyloxycarbonylamino-piperidin-1-yl)-3H-imidazol-4-carboxylate

50 g (0.199 mol) of N-benzyl-N'-cyano-O-phenyl-isourea and 40.056 g (0.2 mol) of 3-
10 tert.-butyloxycarbonylamino-piperidine are heated to 80°C in 50 ml of
dimethylformamide (DMF) for 4 hours. After standing overnight 250 ml of ethyl acetate
are added, the precipitate is suction filtered, washed with ethyl acetate and ether and
dried. More product is obtained from the mother liquor after evaporation and treatment of
the residue with ethyl acetate and ether. Total yield: 48.0 g (67.5% of theory) of N-
15 benzyl-N'-cyano-(3-tert.-butyloxy-carbonylamino-piperidin)-1-carboxamidine.
R_f value: 0.56 (aluminium oxide, methylene chloride/methanol = 40:1)

10.008 g (28 mmol) of this substance are dissolved in 15 ml DMF. After the addition of
4.256 g (30.8 mmol) of potassium carbonate the mixture is treated with ultrasound for
20 three minutes, then 3.416 ml (30.8 mmol) of ethyl bromoacetate are added in one go and
the mixture is stirred for 36 hours at ambient temperature, adding another 10 ml of DMF
after 8 hours for ease of stirring. The reaction mixture is stirred with water, extracted with
ethyl acetate, the organic phase is dried and concentrated by evaporation. The resin
obtained is purified by column chromatography (silica gel, ethyl acetate/petroleum ether
25 = 3:1 to 9:1)

5.4 g (43.5 % of theory) of N-benzyl-N'-cyano-N-ethoxycarbonylmethyl-(3-tert.-
butyloxy-carbonylamino-piperidin)-1-carboxamidine are obtained.

R_f value: 0.7 (silica gel, ethyl acetate/petroleum ether = 4:1)

30 5.1 g (11.498 mmol) of this compound are added batchwise to a solution of 0.785 g
(11.536 mmol) of sodium ethoxide in 25 ml of ethanol. The mixture is stirred for 40

minutes at 60°C, then combined with 50 ml of ethanol and 10 ml of water and cooled. The precipitate is suction filtered and dissolved in methylene chloride. After drying and evaporation of the solvent, 4.8 g (94.1 % of theory) of the title compound is obtained. R_f value: 0.4 (silica gel, ethyl acetate/petroleum ether = 4:1)

5

The following was obtained analogously to Example I:

(1) ethyl 5-amino-3-(3-methyl-but-2-enyl)-2-(3-tert.-butyloxycarbonylamino-piperidin-1-yl)-3H-imidazol-4-carboxylate

10 prepared from diphenyl-N-cyanocarbonimidate, glycine ethylester, (3-tert.-butoxy-carbonylamino)-piperidine and 3-methyl-but-2-en-1-yl-bromide.

R_f value: 0.1-0.2 (silica gel, ethyl acetate/petroleum ether = 1:1)

Example II

15 tert. butyl [1-(7-benzyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]carbaminate
360 mg (0.812 mmol) of ethyl 5-amino-3-benzyl-2-(3-tert.-butoxy-carbonylamino-piperidin-1-yl)-3H-imidazol-4-carboxylate and 131.472 (1.2 mmol) of ethylformate hydrochloride are placed in 1.3 g phenol. A solution of 141.667 mg (2mmol) of sodiummethoxide in 2 ml of tetrahydrofuran (THF) is added dropwise with stirring, the
20 THF is evaporated off and the mixture is kept for 2 hours at 150°C. The brown reaction mixture is purified through a silica gel column. 50 mg (15.7 % of theory) of the title compound were obtained.

melting point: 208°C.

R_f value: 0.15 (silica gel, methylene chloride/methanol = 15:1)

25

Example III

tert. butyl [1-(7-benzyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]carbaminate

30 19 mg (0.138 mmol) of potassium carbonate and then 16 mg (0.113 mmol) of methyl iodide are added to a solution of 42 mg (0.099 mmol) of the compound of Example II in

0.3 ml DMF. The mixture is stirred for 2 hours at ambient temperature, then triturated with water and extracted with ethyl acetate. The organic phase is washed with water and dried with activated charcoal and magnesium sulphate. After evaporation 29 mg (66.8 % of theory) of the title compound is obtained.

5 R_f value: 0.3 (silica gel, methylene chloride/methanol = 15:1)

The following was obtained analogously to Example III:

(1) tert. butyl [1-(7-benzyl-1-{2-oxo-2-phenyl-ethyl}-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

10 prepared from Example II and phenacylbromide.

R_f value: 0.4 (silica gel, methylene chloride/methanol = 15:1)

Example IV

15 tert. butyl [1-(7-benzyl-2-methylsulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

3.186 ml (27 mmol) of ethyloxycarbonyl isothiocyanate are added dropwise to a solution of 10.8 g (24.345 mmol) of the compound of Example I in 45 ml THF. The mixture is heated to boiling for one hour, concentrated by evaporation and the residue is brought to
20 crystallisation by treating with diisopropylether.

13.5 g (96.5 % of theory) of ethyl 3-benzyl-2-(3-tert.-butoxycarbonylamino-piperidin-1-yl)-5-(N'-ethyloxycarbonyl-thioureido)-3H-imidazol-4-carboxylate are obtained.

13 g (22.620 mmol) of this compound are placed in 21 ml of n-butanol. After the addition
25 of 2.536 (22.6 mmol) of potassium-tert.-butoxide the mixture is stirred for 45 minutes at 100°C, during which time a precipitate settles out. After standing overnight at ambient temperature the mixture is combined with ether, suction filtered and dried. 10.6 g (94.7 % of theory) of tert. butyl [1-(7-benzyl-2-mercapto-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate potassium salt are obtained.

30

10.5 g (21.225 mmol) of this compound are suspended in 25 ml of water, and ethanol is added to the solution. After the addition of 2.135 ml (21.515 mmol) of dimethylsulphate the mixture is stirred for 4 hours at ambient temperature. The precipitate is suction filtered, washed with cold ethanol and dried. 8.8 g (88.1 % of theory) of the title compound are obtained.

R_f value: 0.3 (silica gel, methylene chloride/methanol = 20:1)

The following compounds were obtained analogously to Example IV:

- 10 (1) tert. butyl [1-(7-benzyl-2-benzylsulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from compound I, ethyloxycarbonyl isothiocyanate and benzylbromide.

R_f value: 0.65 (silica gel, ethyl acetate/petroleum ether = 2:1)

- 15 (2) tert. butyl [1-(7-allyl-2-methylsulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from compound I.1, ethyloxycarbonyl isothiocyanate and methyl iodide.

R_f value: 0.6 (silica gel, methylene chloride/methanol = 10:1)

- 20 (3) tert. butyl [1-(7-benzyl-2-[2-phenylethyl]sulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from compound I, ethyloxycarbonyl isothiocyanate and 2-phenylethylbromide.

R_f value: 0.65 (silica gel, ethyl acetate/petroleum ether = 2:1)

25 Example V

tert-butyl [1-(7-benzyl-1-methyl-2-methylsulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

- 30 A suspension of 2.5 g (5.312 mmol) of compound IV in 15 ml DMF is combined with 645.15 mg (5.75 mmol) of potassium-tert.-butoxide. 922.605 mg (6.5 mmol) of methyl iodide are added to the resulting solution and the mixture is stirred overnight at ambient

temperature. Water is added and the mixture is extracted with methylene chloride. The organic phase is washed with water, dried and concentrated by evaporation. The residue is crystallised with diisopropylether. 2 g (77.7 % of theory) of the title compound are obtained.

5 R_f value: 0.55 (silica gel, methylene chloride/methanol = 20:1)

The following compounds were obtained analogously to Example V:

(1) tert. butyl [1-(7-benzyl-2-methylsulphanyl-1-phenacyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate
10

prepared from compound IV and phenacylbromide.

R_f value: 0.7 (aluminium oxide, methylene chloride/methanol = 40:1)

(2) tert. butyl [1-(1-methyl-7-(3-methyl-butenyl)-2-methylsulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate
15

prepared from compound IV.1 and methyl iodide.

R_f value: 0.4 (silica gel, methylene chloride/methanol = 20:1)

(3) tert. butyl [1-(1-benzyl-7-benzyl-2-methylsulphanyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate
20

prepared from compound IV and benzylbromide.

R_f value: 0.75 (silica gel, ethyl acetate/petroleum ether = 4:1)

(4) tert. butyl [1-(7-benzyl-2-methylsulphanyl-1-(2-phenylethyl)-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate
25

prepared from compound IV and 2-phenylethylbromide.

R_f value: 0.75 (silica gel, ethyl acetate/petroleum ether = 4:1)

(5) tert. butyl [1-(7-benzyl-2-benzylsulphanyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate
30

prepared from compound IV.1 and methyl iodide.

R_f value: 0.85 (silica gel, ethyl acetate/petroleum ether = 1:2)

(6) tert. butyl [1-(7-benzyl-2-[2-phenylethyl]sulphanyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbamate

5 prepared from compound IV.3 and methyl iodide.

R_f value: 0.65 (silica gel, ethyl acetate/petroleum ether = 1:2)

Example VI

10 tert. butyl [1-(7-benzyl-1-methyl-2-methylsulphinyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbamate and tert. butyl [1-(7-benzyl-1-methyl-2-methylsulphonyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbamate

A solution of 250 mg (0.516 mmol) of compound V in 5 ml of dichloromethane and 0.5 ml of methanol is combined with 120.789 mg (0.7 mmol) of m-chloro-perbenzoic acid
15 with stirring and cooling with ice. After 30 minutes the ice bath is removed and the mixture is stirred overnight at ambient temperature. 50 ml of methylene chloride are added and the mixture is extracted with 10 % soda solution. The organic phase is washed with water, dried and concentrated by evaporation. 220 mg of the two title compounds are obtained in the ratio 45 : 55.

20 R_f value: 0.1 (sulphoxide) and 0.8 (sulphone) (silica gel, ethyl acetate)

The following compounds were obtained analogously to Example VI:

(1) tert. butyl [1-methyl-7-(3-methyl-but-2-enyl)-2-methylsulphinyl-6-oxo-6,7-dihydro-1H-purin-8-yl]-piperidin-3-yl)-carbamate and tert. butyl [1-methyl-7-(3-methyl-but-2-enyl)-2-methylsulphonyl-6-oxo-6,7-dihydro-1H-purin-8-yl]-piperidin-3-yl)-carbamate
25

prepared from compound V.2 and m-chloro-perbenzoic acid. The product obtained after a reaction time of 80 minutes is the sulphoxide, which contains a maximum of 10%
30 sulphone.

R_f value: 0.5 (silica gel, methylene chloride/methanol = 10:1)

(2) tert. butyl [1-(7-benzyl-2-methanesulphonyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from compound V.

5 R_f value: 0.75 (silica gel, ethyl acetate)

Mass spectrum (ESI⁺): $m/z = 517$ [M+H]⁺

Example VII

10 Tert. butyl [1-(7-benzyl-2-benzylamino-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

258.312 mg of the mixture obtained in Example VI and 214.313 mg of benzylamine are stirred for 16 hours at ambient temperature. The mixture is triturated with 20 ml of diisopropylether, the precipitate is suction filtered, dissolved in a little methylene chloride
15 and crystallised with diisopropylether. 250 mg of the title compound are obtained.

R_f value: 0.55 (silica gel, ethyl acetate)

The following compounds were prepared analogously to Example VII:

20 (1) tert. butyl [1-(7-benzyl-2-[4-fluoro-benzyl]amino-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from Example VI and 4-fluoro-benzylamine

R_f value: 0.49 (silica gel, ethyl acetate)

25 (2) tert. butyl [1-(7-benzyl-1-methyl-2-(2-phenylethyl)amino-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from Example VI and 2-(2-phenylethyl)amine.

R_f value: 0.5 (silica gel, ethyl acetate)

30 (3) tert. butyl [1-(7-benzyl-2-isopropylamino-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from Example VI and isopropylamine.

R_f value: 0.6 (silica gel, methylene chloride/methanol = 9:1)

(4) tert. butyl [1-(7-benzyl-1-methyl-2-methylamino-6-oxo-6,7-dihydro-1H-purin-8-yl)-
5 piperidin-3-yl]-carbaminate

prepared from Example VI and methylamine gas.

R_f value: 0.27 (silica gel, methylene chloride/methanol = 19:1)

(5) tert. butyl [1-(7-benzyl-2-cyclohexylamino-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-
10 yl)-piperidin-3-yl]-carbaminate

prepared from Example VI and cyclohexylamine

R_f value: 0.65 (silica gel, methylene chloride/methanol = 9:1)

(6) tert. butyl [1-(7-benzyl-2-cyclohexylmethylamino-1-methyl-6-oxo-6,7-dihydro-1H-
15 purin-8-yl)-piperidin-3-yl]-carbaminate

prepared from Example VI and cyclohexylmethylamine.

R_f value: 0.54 (silica gel, ethyl acetate)

(7) tert. butyl [1-(7-benzyl-1-methyl-2-piperidino-6-oxo-6,7-dihydro-1H-purin-8-yl)-
20 piperidin-3-yl]-carbaminate

prepared from Example VI and piperidine.

R_f value: 0.45 (silica gel, methylene chloride/methanol = 20:1)

(8) tert. butyl [1-(7-benzyl-2-dimethylamino-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-
25 yl)-piperidin-3-yl]-carbaminate

prepared from Example VI and dimethylamine

R_f value: 0.65 (silica gel, methylene chloride/methanol = 9:1)

(9) tert. butyl [1-(2-amino-7-benzyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-
30 piperidin-3-yl]-carbaminate

prepared from Example VI and ammonia gas.

R_f value: 0.4 (silica gel, methylene chloride/methanol = 10:1)

(10) tert. butyl [1-(2-benzylamino-1-methyl-7-[3-methylbut-2-enyl]-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidino-3-yl]-carbamate

5 prepared from Example VI.1 and benzylamine

R_f value: 0.6 (silica gel, ethyl acetate)

Example VIII

10 Tert. butyl [1-(7-benzyl-1-methyl-2-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbamate

A solution of 258.32 mg of Example VI in 3 ml of THF is combined with 0.2 ml of a 3-molar solution of methylmagnesium bromide in ether and the mixture is stirred for 48 hours at ambient temperature. 50 ml of ether were added and the mixture was extracted with water at pH 4. The organic phase was dried and concentrated by evaporation. The product obtained was purified through a silica gel column. 55 mg of the title compound are obtained.

R_f value: 0.55 (silica gel, methylene chloride/methanol = 10:1)

20 The following compound was obtained analogously to Example VIII:

(1) tert. butyl [1-(1-methyl-7-[3-methyl-but-2-enyl]-2-[2-phenylethyl]-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbamate

prepared from Example VI.1 and (2-phenylethyl)magnesium bromide.

R_f value: 0.5 (silica gel; methylene chloride/methanol = 10:1)

25

Example IX

Tert. butyl {1-[7-benzyl-1-methyl-6-oxo-2-(2-oxo-2-phenyl-ethyl)-6,7-dihydro-1H-purin-8-yl]-piperidin-3-yl}-carbamate

30 A solution of 132 mg of acetophenone in 1 ml of tetrahydrofuran is added dropwise at 0°C to a solution of 0.63 ml of n-butyllithium (1.6 M in n-hexane) and 119 mg

diisopropylamine in 2 ml of tetrahydrofuran. After 15 minutes a solution of 500 mg of tert. butyl [1-(7-benzyl-2-methanesulphonyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate in 2 ml of tetrahydrofuran is added dropwise. Then the cooling bath is removed and the reaction mixture is stirred overnight at ambient
5 temperature. As the thin layer chromatograph shows that there is still some starting material present, a further 0.94 ml of n-butyllithium (1.6 M in n-hexane) are added. After another 24 hours the reaction solution is diluted with 50 ml of water, adjusted to pH 6 with 2 N hydrochloric acid and extracted with ethyl acetate. The combined organic phases are washed with water, dried over magnesium sulphate and evaporated down. The crude
10 product is purified by chromatography over a silica gel column with methylene chloride as eluant. 54 mg of the title compound are obtained.
R_f value: 0.55 (aluminium oxide, methylene chloride)
Mass spectrum (ESI⁺): m/z = 557 [M+H]⁺

15 Example X

Tert. butyl [1-(7-benzyl-2-cyano-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate
268 mg of tetrabutylammonium cyanide are added to 258 mg of tert. butyl [1-(7-benzyl-2-
20 methanesulphonyl-1-methyl-6-oxo-6,7-dihydro-1H-purin-8-yl)-piperidin-3-yl]-carbaminate in 1 ml of methylene chloride and the reaction mixture is stirred for two days at ambient temperature. The reaction solution is chromatographed through a silica gel column with methylene chloride/methanol (97:3 to 90:1) as eluant. The product thus obtained is crystallised from diisopropylether.
25 126 mg of the title compound are obtained.
R_f value: 0.75 (silica gel, methylene chloride/methanol = 10:1)
Mass spectrum (ESI⁺): m/z = 464 [M+H]⁺

30 Example XI

Tert. butyl {1-[1-benzyl-2-methyl-7-(3-methyl-but-2-enyl)-6-oxo-6,7-dihydro-1H-purin-8-yl]-piperidin-3-yl}-carbaminat

A mixture of 105 mg of tert. butyl {1-[5-methyl-1-(3-methyl-but-2-enyl)-7-oxo-1,7-dihydro-imidazo[4,5-d][1,3]oxazin-2-yl]-piperidin-3-yl}-carbaminat and 40 μ l benzylamine in 1.5 ml of methylene chloride is stirred for two days at 40°C. Then 57 μ l triethylamine and 37 μ l phosphorus oxychloride are added and the reaction mixture is stirred for a further six hours at 40°C. For working up the reaction mixture is combined with aqueous potassium carbonate solution and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulphate and evaporated down. The crude product is purified by chromatography over a silica gel column with methylene chloride/methanol (1:0 to 20:1) as eluant. 30 mg of the title compound are obtained. Mass spectrum (ESI⁺): m/z = 507 [M+H]⁺

The following is obtained analogously to Example XI:

(1) tert. butyl (1-{1-[(naphthalen-1-yl)methyl]-2-methyl-7-(3-methyl-but-2-enyl)-6-oxo-6,7-dihydro-1H-purin-8-yl}-piperidin-3-yl)-carbaminat prepared from Example XII and 1-aminomethyl-naphthalene. Mass spectrum (ESI⁺): m/z = 557 [M+H]⁺

Example XII

Tert. butyl {1-[5-methyl-1-(3-methyl-but-2-enyl)-7-oxo-1,7-dihydro-imidazo[4,5-d][1,3]oxazin-2-yl]-piperidin-3-yl}-carbaminat

A mixture of 1.0 g of ethyl 5-acetylamino-2-(3-tert.-butyloxycarbonylamino-piperidin-1-yl)-3-(3-methyl-but-2-enyl)-3H-imidazol-4-carboxylate, 566 mg of triphenylphosphine and 0.97 ml of triethylamine in 16 ml of toluene is heated to 80°C and combined with a solution of 702 mg of 1,2-dibromo-tetrachloroethane in 8 ml of toluene. The reaction mixture is stirred for four hours at 80°C, then the precipitate formed is filtered off and washed with toluene. The filtrate is evaporated down in vacuo and chromatographed

through a silica gel column with cyclohexane/ethyl acetate as eluant. 804 mg of the title compound are obtained.

Mass spectrum (ESI⁺): m/z = 418 [M+H]⁺

- 5 The following compound is obtained from Example XIII.1 under the same reaction conditions:

(1) ethyl 2 -(3-tert.-butyloxycarbonylamino-piperidin-1-yl)-5-isocyano-3-(3-methyl-but-2-enyl)-3H-imidazol-4-carboxylate

Mass spectrum (ESI⁺): m/z = 432 [M+H]⁺

10

Example XIII

Ethyl 5-acetylamino-2-(3-tert.-butyloxycarbonylamino-piperidin-1-yl)-3-(3-methyl-but-2-enyl)-3H-imidazol-4-carboxylate

- 15 prepared from Example I.1 by reaction with acetylchloride in the presence of pyridine in methylene chloride.

Mass spectrum (ESI⁺): m/z = 464 [M+H]⁺

The following compound is obtained analogously to Example XIII:

20

(1) ethyl 2-(3-tert.-butyloxycarbonylamino-piperidin-1-yl)-5-formylamino-3-(3-methyl-but-2-enyl)-3H-imidazol-4-carboxylate

prepared from Example I.1 by reaction with formic acid and acetic anhydride in the presence of pyridine in methylene chloride.

- 25 Mass spectrum (ESI⁺): m/z = 450 [M+H]⁺

Example XIV

Tert. butyl (1-{1-[(naphthalen-1-yl)methyl]-7-(3-methyl-but-2-enyl)-6-oxo-6,7-dihydro-1H-purin-8-yl}-piperidin-3-yl)-carbaminate

30

210 mg of 1-aminomethyl-naphthalene and 30 mg of copper(I)oxide are added to 295 mg of ethyl 2-(3-tert.-butoxycarbonylamino-piperidin-1-yl)-5-isocyano-3-(3-methyl-but-2-enyl)-3H-imidazol-4-carboxylate in 7 ml of toluene. The reaction mixture is stirred for 10 hours at 120°C. After cooling to ambient temperature it is diluted with ethyl acetate and filtered through Celite. The filtrate is combined with water and extracted with ethyl acetate. The combined extracts are dried over magnesium sulphate and evaporated down. The crude product is chromatographed through a silica gel column with methylene chloride/methanol (1:0 to 10:1) as eluant. 306 mg of the title compound are obtained, contaminated with ethyl 5-amino-2-(3-tert.-butoxycarbonylamino-piperidin-1-yl)-3-(3-methyl-but-2-enyl)-3H-imidazol-4-carboxylate.

Mass spectrum (ESI⁺): m/z = 543 [M+H]⁺

The following compound is obtained analogously to Example XIV:

(1) tert. butyl (1-{1-[(4-methoxy-naphthalen-1-yl)methyl]-7-(3-methyl-but-2-enyl)-6-oxo-6,7-dihydro-1H-purin-8-yl}-piperidin-3-yl)-carbaminate prepared from Example XII.1 and 1-aminomethyl-4-methoxy-naphthalene.

R_f value: 0.17 (silica gel, cyclohexane/ethyl acetate = 1:9)

Mass spectrum (ESI⁺): m/z = 573 [M+H]⁺

Examples of the preparation of the end products:

Example 1

8-(3-amino-piperidin-1-yl)-7-benzyl-2-benzylamino-1-methyl-1,7-dihydro-purin-6-one

A solution of 200 mg of Example VII in 2 ml of dichloromethane is combined with 3 ml of trifluoroacetic acid with stirring and cooling with ice. After 30 minutes the ice bath is removed and stirring is continued for 2 hours. The solvent is evaporated at low temperature, the residue is triturated with ether, suction filtered and dried in vacuo. 150 mg (73.1 % of theory) of the trifluoroacetate of the title compound are obtained.

R_f value: 0.45 (aluminium oxide, methylene chloride/methanol = 20:1)

¹H-NMR spectrum (400 MHz, DMSO-d₆):

1.5 (m,2H), 1,7 (m,1H), 1.95 (m,1H), 2.8 (m,1H), 3.0 (m,1H), 3.15 (d,1H), 3.4 (s+m,4H),
3.5(d,1H), 4.55 (d,2H), 5.35(s,2H), 7.1-7.5 (m,12H), 8.0 (s,3H), 8.1-8.3 (m,1H)

5

The following compounds were obtained analogously to Example 1:

(1) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-(4-fluoro-benzylamino)-1-methyl-1,7-dihydro-purin-6-one trifluoroacetate

10 prepared from Example VII.1 and trifluoroacetic acid

R_f value: 0.69 (aluminium oxide, methylene chloride/methanol = 9:1)

(2) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-phenylethyl)amino]-1,7-dihydro-purin-6-one trifluoroacetate

15 prepared from Example VII.2 and trifluoroacetic acid.

R_f value: 0.75 (aluminium oxide, methylene chloride/methanol = 9:1)

(3) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-isopropylamino-1-methyl-1,7-dihydro-purin-6-one trifluoroacetate

20 prepared from Example VII.3 and trifluoroacetic acid.

R_f value: 0.68 (aluminium oxide, methylene chloride/methanol = 9:1)

(4) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-methylamino-1,7-dihydro-purin-6-one trifluoroacetate

25 prepared from Example VII.4 and trifluoroacetic acid.

R_f value: 0.26 (aluminium oxide, methylene chloride/methanol = 9:1)

(5) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-cyclohexylamino-1-methyl-1,7-dihydro-purin-6-one trifluoroacetate

30 prepared from Example VII.5 and trifluoroacetic acid.

R_f value: 0.65 (aluminium oxide, methylene chloride/methanol = 9:1)

(6) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-cyclohexylmethylamino-1-methyl-1,7-dihydro-purin-6-one trifluoroacetate
prepared from Example VII.6 and trifluoroacetic acid.

5 R_f value: 0.69 (aluminium oxide, methylene chloride/methanol = 9:1)

(7) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(piperidin-1-yl)-1,7-dihydro-purin-6-one hydrochloride
prepared from Example VII.7 and hydrogen chloride in dioxane.

10 R_f value: 0.3-0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

(8) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-dimethylamino-1-methyl-1,7-dihydro-purin-6-one trifluoroacetate
prepared from Example VII.8 and trifluoroacetic acid.

15 R_f value: 0.69 (aluminium oxide, methylene chloride/methanol = 9:1)

(9) 2-amino-8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-1,7-dihydro-purin-6-one trifluoroacetate
prepared from Example VII.9 and trifluoroacetic acid.

20 R_f value: 0.2 (aluminium oxide, methylene chloride/methanol = 10:1)

(10) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-methyl-but-2-en-1-yl)-1,7-dihydro-purin-6-one trifluoroacetate
prepared from Example VII.10 and trifluoroacetic acid.

25 R_f value: 0.55 (aluminium oxide, methylene chloride/methanol = 10:1)

(11) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-methyl-1,7-dihydro-purin-6-one trifluoroacetate
prepared from Example VIII and trifluoroacetic acid.

30 R_f value: 0.6 (aluminium oxide, methylene chloride/methanol = 10:1)

(12) 8-(3-amino-piperidin-1-yl)-1-methyl-7-(3-methyl-but-2-en-1-yl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one trifluoroacetate

prepared from Example VIII.1 and trifluoroacetic acid.

R_f value: 0.4 (aluminium oxide, methylene chloride/methanol = 20:1)

5

(13) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-1,7-dihydro-purin-6-one hydrochloride

prepared from Example III and hydrogen chloride in dioxane.

R_f value: 0.2-0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

10

(14) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-methylsulphanyl-1,7-dihydro-purin-6-one hydrochloride

prepared from Example IV and hydrogen chloride in dioxane.

R_f value: 0.5 (aluminium oxide, methylene chloride/methanol = 10:1)

15

(15) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-benzylsulphanyl-1,7-dihydro-purin-6-one trifluoroacetate

prepared from Example IV.1 and trifluoroacetic acid.

R_f value: 0.5-0.6 (aluminium oxide, methylene chloride/methanol = 10:1)

20

(16) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-methylsulphanyl-1,7-dihydro-purin-6-one hydrochloride

prepared from Example V and hydrogen chloride in dioxane.

R_f value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

25

(17) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-methylsulphanyl-1-(2-phenyl-2-oxo-ethyl)-1,7-dihydro-purin-6-one hydrochloride

prepared from Example V.1 and hydrogen chloride in dioxane.

R_f value: 0.4 (aluminium oxide, methylene chloride/methanol = 20:1)

30

(18) 8-(3-amino-piperidin-1-yl)-1-benzyl-7-benzyl-2-methylsulphanyl-1,7-dihydro-purin-6-one hydrochloride

prepared from Example V.3 and hydrogen chloride.

R_f value: 0.4-0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

5

(19) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-methylsulphanyl-1-(2-phenylethyl)-1,7-dihydro-purin-6-one hydrochloride

prepared from Example V.4 and hydrogen chloride.

R_f value: 0.4 (aluminium oxide, methylene chloride/methanol = 20:1)

10

(20) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-benzylsulphanyl-1-methyl-1,7-dihydro-purin-6-one

prepared from Example V.5 and hydrogen chloride.

R_f value: 0.5 (aluminium oxide, methylene chloride/methanol = 20:1)

15

(21) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-[(2-phenylethyl)sulphanyl]-1-methyl-1,7-dihydro-purin-6-one

prepared from Example V.6 and hydrogen chloride.

R_f value: 0.55 (aluminium oxide, methylene chloride/methanol = 20:1)

20

(22) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-oxo-2-phenyl-ethyl)-1,7-dihydro-purin-6-one trifluoroacetate

prepared from Example III.1 and trifluoroacetic acid.

R_f value: 0.65 (aluminium oxide, methylene chloride/methanol = 10:1)

25

(23) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-oxo-2-phenyl-ethyl)-1,7-dihydro-purin-6-one

prepared from Example IX and trifluoroacetic acid.

R_f value: 0.20 (silica gel, methylene chloride/methanol = 10:1)

30

Mass spectrum (ESI⁺): m/z = 457 [M+H]⁺

(24) 8-(3-amino-piperidin-1-yl)-7-benzyl-2-cyano-1-methyl-1,7-dihydro-purin-6-one
trifluoroacetate

prepared from Example X and trifluoroacetic acid.

R_f value: 0.50 (aluminium oxide, methylene chloride/methanol = 20:1)

5 Mass spectrum (ESI⁺): m/z = 364 [M+H]⁺

(25) 8-(3-amino-piperidin-1-yl)-1-benzyl-2-methyl-7-(3-methyl-but-2-en-1-yl)-1,7-
dihydro-purin-6-one

prepared from Example XI and trifluoroacetic acid.

10 Mass spectrum (ESI⁺): m/z = 407 [M+H]⁺

(26) 8-(3-amino-piperidin-1-yl)-2-methyl-7-(3-methyl-but-2-en-1-yl)-1-[(naphthalen-1-
yl)methyl]-1,7-dihydro-purin-6-one

prepared from Example XI.1 and trifluoroacetic acid.

15 Mass spectrum (ESI⁺): m/z = 457 [M+H]⁺

(27) 8-(3-amino-piperidin-1-yl)-7-(3-methyl-but-2-en-1-yl)-1-[(naphthalen-1-yl)methyl]-
1,7-dihydro-purin-6-one

prepared from Example XIV and trifluoroacetic acid.

20 Mass spectrum (ESI⁺): m/z = 443 [M+H]⁺

(28) 8-(3-amino-piperidin-1-yl)-7-(3-methyl-but-2-en-1-yl)-1-[(4-methoxy-naphthalen-1-
yl)methyl]-1,7-dihydro-purin-6-one

prepared from Example XIV.1 and trifluoroacetic acid.

25 Mass spectrum (ESI⁺): m/z = 473 [M+H]⁺

The following compounds may also be obtained analogously to the preceding Examples
and other methods known from the literature:

30

(1) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-ethyl-2-benzylamino-1,7-dihydro-purin-6-one

- (2) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-propyl-2-benzylamino-1,7-dihydro-purin-6-one
- 5 (3) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-isopropyl-2-benzylamino-1,7-dihydro-purin-6-one
- (4) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-butyl-2-benzylamino-1,7-dihydro-purin-6-one
- 10 (5) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-methyl-propyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (6) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-pentyl-2-benzylamino-1,7-dihydro-purin-6-one
- 15 (7) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-methyl-butyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (8) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-hexyl-2-benzylamino-1,7-dihydro-purin-6-one
- 20 (9) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4-methyl-pentyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (10) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-allyl-2-benzylamino-1,7-dihydro-purin-6-one
- 25 (11) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-methyl-but-2-en-1-yl)-2-benzylamino-1,7-dihydro-purin-6-one
- (12) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(prop-2-in-1-yl)-2-benzylamino-1,7-dihydro-purin-6-one
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- (13) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-cyclopropylmethyl-2-benzylamino-1,7-dihydro-purin-6-one
- (14) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-cyclohexylmethyl-2-benzylamino-1,7-dihydro-purin-6-one
- (15) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4-chlorobenzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (16) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-fluorobenzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (17) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4-methylbenzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (18) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2,4-dimethylbenzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (19) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2,4-dimethoxybenzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (20) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-trifluoromethyl-benzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (21) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-trifluoromethoxy-benzyl)-2-benzylamino-1,7-dihydro-purin-6-one
- (22) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-difluoromethoxy-benzyl)-2-benzylamino-1,7-dihydro-purin-6-one

(23) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(furan-2-yl-methyl)-2-benzylamino-1,7-dihydro-purin-6-one

5 (24) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(thien-2-yl-methyl)-2-benzylamino-1,7-dihydro-purin-6-one

(25) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-methyl-isoxazol-5-yl-methyl)-2-benzylamino-1,7-dihydro-purin-6-one

10 (26) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(pyridin-4-yl-methyl)-2-benzylamino-1,7-dihydro-purin-6-one

(27) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-methyl-phenyl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

15 (28) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2,4-dichloro-phenyl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

(29) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

(30) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

25 (31) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-trifluoromethoxy-phenyl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

(32) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-difluoromethoxy-phenyl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

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(33) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(furan-2-yl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

5 (34) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(thien-2-yl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

(35) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(pyridin-3-yl)-2-oxo-ethyl]-2-benzylamino-1,7-dihydro-purin-6-one

10 (36) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-oxopropyl)-2-benzylamino-1,7-dihydro-purin-6-one

(37) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-benzylamino-1,7-dihydro-purin-6-one

15 (38) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-ethyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(39) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-propyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

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(40) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-isopropyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

25 (41) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-butyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(42) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-methyl-propyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

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(43) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-pentyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

5 (44) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-methyl-butyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(45) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-hexyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

10 (46) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4-methyl-pentyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(47) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-allyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

15 (48) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-methyl-but-2-en-1-yl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

20 (49) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(prop-2-in-1-yl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(50) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-cyclopropylmethyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

25 (51) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-cyclohexylmethyl-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(52) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4-chlorobenzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

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- (53) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-fluorobenzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (54) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4-methylbenzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (55) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2,4-dimethylbenzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (56) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2,4-dimethoxybenzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (57) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-trifluoromethyl-benzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (58) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-trifluoromethoxy-benzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (59) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-difluoromethoxy-benzyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (60) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(furan-2-yl-methyl)-2-(2-phenylethyl)-7-dihydro-purin-6-one
- (61) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(thien-2-yl-methyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one
- (62) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(3-methyl-isoxazol-5-yl-methyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(63) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(pyridin-4-yl-methyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

5 (64) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-methyl-phenyl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(65) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2,4-dichloro-phenyl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

10 (66) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-methoxy-phenyl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(67) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-trifluoromethyl-phenyl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

15 (68) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-trifluoromethoxy-phenyl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

20 (69) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(4-difluoromethoxy-phenyl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(70) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(furan-2-yl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

25 (71) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(thien-2-yl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(72) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(pyridin-3-yl)-2-oxo-ethyl]-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

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(73) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-oxo-propyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

5 (74) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-cyclohexyl-2-oxo-ethyl)-2-(2-phenylethyl)-1,7-dihydro-purin-6-one

(75) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-ethylamino-1,7-dihydro-purin-6-one

10 (76) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-propylamino-1,7-dihydro-purin-6-one

(77) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-butylamino-1,7-dihydro-purin-6-one

15 (78) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-methyl-propylamino)-1,7-dihydro-purin-6-one

(79) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(N-ethyl-N-methyl-amino)-1,7-dihydro-purin-6-one

(80) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-diethylamino-1,7-dihydro-purin-6-one

25 (81) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(N-methyl-N-propyl-amino)-1,7-dihydro-purin-6-one

(82) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(N-butyl-N-methyl-amino)-1,7-dihydro-purin-6-one

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(83) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-hydroxyethyl-amino)-1,7-dihydro-purin-6-one

5 (84) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[N-methyl-N-(2-hydroxyethyl)-amino]-1,7-dihydro-purin-6-one

(85) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-methoxy-ethylamino)-1,7-dihydro-purin-6-one

10 (86) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-methoxy-propylamino)-1,7-dihydro-purin-6-one

(87) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[N-methyl-N-(2-methoxy-ethyl)-amino]-1,7-dihydro-purin-6-one

15 (88) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-phenoxyethyl)-amino]-1,7-dihydro-purin-6-one

20 (89) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-aminoethyl)-amino]-1,7-dihydro-purin-6-one

(90) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(3-aminopropyl)-amino]-1,7-dihydro-purin-6-one

25 (91) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-methylamino-ethyl)-amino]-1,7-dihydro-purin-6-one

(92) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(3-dimethylamino-propyl)amino]-1,7-dihydro-purin-6-one

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(93) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-acetylamino-ethyl)amino]-1,7-dihydro-purin-6-one

5 (94) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-benzoylamino-ethyl)amino]-1,7-dihydro-purin-6-one

(95) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-ethoxycarbonylamino-ethyl)amino]-1,7-dihydro-purin-6-one

10 (96) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-methylsulphanyl-ethyl)amino]-1,7-dihydro-purin-6-one

(97) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-phenylsulphanyl-ethyl)amino]-1,7-dihydro-purin-6-one

15 (98) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-cyano-ethyl)amino]-1,7-dihydro-purin-6-one

(99) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(carboxymethyl)amino]-1,7-dihydro-purin-6-one

(100) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(ethoxycarbonylmethyl)amino]-1,7-dihydro-purin-6-one

25 (101) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(aminocarbonylmethyl)amino]-1,7-dihydro-purin-6-one

(102) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(ethylaminocarbonylmethyl)amino]-1,7-dihydro-purin-6-one

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(103) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(dimethylaminocarbonylmethyl)-amino]-1,7-dihydro-purin-6-one

5 (104) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(pyrrolidin-1-yl-carbonylmethyl)-amino]-1,7-dihydro-purin-6-one

(105) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(piperidin-1-yl-carbonylmethyl)amino]-1,7-dihydro-purin-6-one

10 (106) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(morpholin-4-ylcarbonylmethyl)amino]-1,7-dihydro-purin-6-one

(107) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(cyclopentylmethyl)amino]-1,7-dihydro-purin-6-one

15 (108) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(cyclobutylmethyl)amino]-1,7-dihydro-purin-6-one

20 (109) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(cyclopropylmethyl)amino]-1,7-dihydro-purin-6-one

(110) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-cyclohexyl-ethyl)amino]-1,7-dihydro-purin-6-one

25 (111) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(3-cyclohexyl-propyl)amino]-1,7-dihydro-purin-6-one

(112) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(cyclobutylamino)-1,7-dihydro-purin-6-one

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(113) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(cyclopentylamino)-1,7-dihydro-purin-6-one

5 (114) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(phenylamino)-1,7-dihydro-purin-6-one

(115) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3,4-dichlorobenzyl-amino)-1,7-dihydro-purin-6-one

10 (116) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-methylbenzyl-amino)-1,7-dihydro-purin-6-one

(117) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-methoxybenzyl-amino)-1,7-dihydro-purin-6-one

15 (118) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-trifluoromethylbenzyl-amino)-1,7-dihydro-purin-6-one

20 (119) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-trifluoromethoxybenzyl-amino)-1,7-dihydro-purin-6-one

(120) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-difluoromethoxybenzyl-amino)-1,7-dihydro-purin-6-one

25 (121) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3,4-methylenedioxybenzyl-amino)-1,7-dihydro-purin-6-one

(122) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(furan-2-yl-methyl)amino]-1,7-dihydro-purin-6-one

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(123) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(thien-2-yl-methyl)amino]-1,7-dihydro-purin-6-one

5 (124) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(pyridine-2-yl-methyl)amino]-1,7-dihydro-purin-6-one

(125) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(4-methylthiazol-2-ylmethyl)-amino]-1,7-dihydro-purin-6-one

10 (126) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[[2-(pyridine-2-yl)ethyl]amino]-1,7-dihydro-purin-6-one

(127) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(pyrrolidin-1-yl)-1,7-dihydro-purin-6-one

15 (128) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(morpholin-4-yl)-1,7-dihydro-purin-6-one

(129) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(piperazin-1-yl)-1,7-dihydro-
20 purin-6-one

(130) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-methyl-piperazin-1-yl)-1,7-dihydro-purin-6-one

25 (131) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-ethyl-1,7-dihydro-purin-6-one

(132) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-propyl-1,7-dihydro-purin-6-one

(133) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-isopropyl-1,7-dihydro-purin-6-one
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(134) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-butyl-1,7-dihydro-purin-6-one

- (135) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-methyl-propyl)-1,7-dihydro-purin-6-one
- 5 (136) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-pentyl-1,7-dihydro-purin-6-one
- (137) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-methyl-butyl)-1,7-dihydro-purin-6-one
- 10 (138) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-hexyl-1,7-dihydro-purin-6-one
- (139) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-methyl-pentyl)-1,7-dihydro-purin-6-one
- 15 (140) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-allyl-1,7-dihydro-purin-6-one
- (141) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-methyl-but-2-en-1-yl)-1,7-dihydro-purin-6-one
- 20 (142) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(hex-5-en-1-yl)-1,7-dihydro-purin-6-one
- (143) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(pent-4-en-1-yl)-1,7-dihydro-purin-6-one
- 25 (144) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(prop-2-yn-1-yl)-1,7-dihydro-purin-6-one
- (145) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-phenylethenyl)-1,7-dihydro-purin-6-one
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(146) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(4-methyl-phenyl)ethenyl]-1,7-dihydro-purin-6-one

5 (147) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-chloro-phenyl)ethenyl]-1,7-dihydro-purin-6-one

(148) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3-fluoro-phenyl)ethenyl]-1,7-dihydro-purin-6-one

10 (149) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3,4-dimethoxy-phenyl)-ethenyl]-1,7-dihydro-purin-6-one

(150) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3-chloro-phenyl)ethenyl]-1,7-dihydro-purin-6-one

15 (151) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3-trifluoromethyl-phenyl)-ethenyl]-1,7-dihydro-purin-6-one

20 (152) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3-trifluoromethoxy-phenyl)-ethenyl]-1,7-dihydro-purin-6-one

(153) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-phenyl-prop-2-en-1-yl)-1,7-dihydro-purin-6-one

25 (154) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-benzyl-1,7-dihydro-purin-6-one

(155) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-phenyl-1,7-dihydro-purin-6-one

30 (156) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-phenyl-propyl)-1,7-dihydro-purin-6-one

- (157) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(4-fluoro-benzyl)-1,7-dihydro-purin-6-one
- (158) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-trifluoromethyl-benzyl)-1,7-dihydro-purin-6-one
- (159) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-chloro-benzyl)-1,7-dihydro-purin-6-one
- (160) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-bromo-benzyl)-1,7-dihydro-purin-6-one
- (161) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-trifluoromethoxy-benzyl)-1,7-dihydro-purin-6-one
- (162) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(3-methoxy-benzyl)-1,7-dihydro-purin-6-one
- (163) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3-chloro-phenyl)ethyl]-1,7-dihydro-purin-6-one
- (164) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-fluoro-phenyl)ethyl]-1,7-dihydro-purin-6-one
- (165) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(4-methyl-phenyl)ethyl]-1,7-dihydro-purin-6-one
- (166) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(4-fluoro-phenyl)ethyl]-1,7-dihydro-purin-6-one

(167) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(3-trifluoromethyl-phenyl)-ethyl]-1,7-dihydro-purin-6-one

5 (168) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-cyclopentyl-1,7-dihydro-purin-6-one

(169) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-cyclohexyl-1,7-dihydro-purin-6-one

10 (170) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(cyclohexylmethyl)-1,7-dihydro-purin-6-one

(171) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(cyclopentylmethyl)-1,7-dihydro-purin-6-one

15 (172) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(2-cyclohexyl-ethyl)-1,7-dihydro-purin-6-one

20 (173) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(furan-2-yl)-1,7-dihydro-purin-6-one

(174) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(thien-2-yl)-1,7-dihydro-purin-6-one

25 (175) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(pyridin-2-yl)-1,7-dihydro-purin-6-one

(176) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(pyridin-4-yl)-1,7-dihydro-purin-6-one

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- (177) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(furan-2-yl-methyl)-1,7-dihydro-purin-6-one
- (178) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(thien-2-yl-methyl)-1,7-dihydro-purin-6-one
- (179) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-(pyridin-2-yl-methyl)-1,7-dihydro-purin-6-one
- (180) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(furan-2-yl)ethyl]-1,7-dihydro-purin-6-one
- (181) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(pyridin-2-yl)ethyl]-1,7-dihydro-purin-6-one
- (182) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[3-(furan-2-yl)propyl]-1,7-dihydro-purin-6-one
- (183) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[3-(pyridin-2-yl)propyl]-1,7-dihydro-purin-6-one
- (184) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-chloro-but-2-en-1-yl)-1,7-dihydro-purin-6-one
- (185) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-chloro-prop-2-en-1-yl)-1,7-dihydro-purin-6-one
- (186) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-trifluoromethyl-3-chloro-prop-2-en-1-yl)-1,7-dihydro-purin-6-one

(187) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3,3-dichloro-prop-2-en-1-yl)-1,7-dihydro-purin-6-one

5 (188) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(but-2-yn-1-yl)-1,7-dihydro-purin-6-one

(189) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(cyclohex-1-en-1-yl-methyl)-1,7-dihydro-purin-6-one

10 (190) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(cyclohexylmethyl)-1,7-dihydro-purin-6-one

(191) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(4-fluoro-benzyl)-1,7-dihydro-purin-6-one

15 (192) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(2-chloro-benzyl)-1,7-dihydro-purin-6-one

20 (193) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-bromo-benzyl)-1,7-dihydro-purin-6-one

(194) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-methyl-benzyl)-1,7-dihydro-purin-6-one

25 (195) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-trifluoromethyl-benzyl)-1,7-dihydro-purin-6-one

(196) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(2-cyano-benzyl)-1,7-dihydro-purin-6-one

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(197) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(2-methoxy-benzyl)-1,7-dihydro-purin-6-one

5 (198) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-trifluoromethoxy-benzyl)-1,7-dihydro-purin-6-one

(199) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3-difluoromethoxy-benzyl)-1,7-dihydro-purin-6-one

10 (200) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(3,4-difluoro-benzyl)-1,7-dihydro-purin-6-one

(201) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(naphth-1-yl-methyl)-1,7-dihydro-purin-6-one

15 (202) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(furan-2-yl-methyl)-1,7-dihydro-purin-6-one

20 (203) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(thien-2-yl-methyl)-1,7-dihydro-purin-6-one

(204) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(pyridin-2-yl-methyl)-1,7-dihydro-purin-6-one

25 (205) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-chloro-but-2-en-1-yl)-1,7-dihydro-purin-6-one

(206) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-chloro-prop-2-en-1-yl)-1,7-dihydro-purin-6-one

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- (207) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-trifluoromethyl-3-chloro-prop-2-en-1-yl)-1,7-dihydro-purin-6-one
- 5 (208) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3,3-dichloro-prop-2-en-1-yl)-1,7-dihydro-purin-6-one
- (209) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(but-2-yn-1-yl)-1,7-dihydro-purin-6-one
- 10 (210) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(cyclohex-1-en-1-yl-methyl)-1,7-dihydro-purin-6-one
- (211) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(cyclohexylmethyl)-1,7-dihydro-purin-6-one
- 15 (212) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(4-fluoro-benzyl)-1,7-dihydro-purin-6-one
- (213) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(2-chloro-benzyl)-1,7-dihydro-purin-6-one
- 20 (214) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-bromo-benzyl)-1,7-dihydro-purin-6-one
- (215) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-methyl-benzyl)-1,7-dihydro-purin-6-one
- 25 (216) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-trifluoromethyl-benzyl)-1,7-dihydro-purin-6-one

(217) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(2-cyano-benzyl)-1,7-dihydro-purin-6-one

5 (218) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(2-methoxy-benzyl)-1,7-dihydro-purin-6-one

(219) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-trifluoromethoxy-benzyl)-1,7-dihydro-purin-6-one

10 (220) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3-difluoromethoxy-benzyl)-1,7-dihydro-purin-6-one

(221) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(3,4-difluoro-benzyl)-1,7-dihydro-purin-6-one

15 (222) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(naphth-1-yl-methyl)-1,7-dihydro-purin-6-one

(223) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(furan-2-yl-methyl)-1,7-dihydro-purin-6-one

(224) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(thien-2-yl-methyl)-1,7-dihydro-purin-6-one

25 (225) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-(pyridin-2-yl-methyl)-1,7-dihydro-purin-6-one

(226) 8-(3-amino-piperidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(227) 8-(3-amino-pyrrolidin-1-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(228) 8-(piperidin-3-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(229) 8-(piperidin-4-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(230) 8-(3-amino-hexahydroazepin-1-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(231) 8-(4-amino-hexahydroazepin-1-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(232) 8-(piperazin-1-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(233) 8-(1,4-diazepan-1-yl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(234) 8-(2-amino-cyclohexylamino)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(235) 8-(3-amino-cyclohexyl)-2-benzylamino-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(236) 8-(3-amino-pyrrolidin-1-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(237) 8-(piperidin-3-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(238) 8-(piperidin-4-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

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(239) 8-(3-amino-hexahydroazepin-1-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

5 (240) 8-(4-amino-hexahydroazepin-1-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(241) 8-(piperazin-1-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

10 (242) 8-(1,4-diazepan-1-yl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

(243) 8-(2-amino-cyclohexylamino)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

15 (244) 8-(3-amino-cyclohexyl)-2-(2-phenylethyl)-1-methyl-7-benzyl-1,7-dihydro-purin-6-one

20 (245) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(but-2-en-1-yl)-1,7-dihydro-purin-6-one

(246) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(2-methyl-but-2-en-1-yl)-1,7-dihydro-purin-6-one

25 (247) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(2,3-dimethyl-but-2-en-1-yl)-1,7-dihydro-purin-6-one

(248) 8-(3-amino-piperidin-1-yl)-2-benzylamino-1-methyl-7-(cyclopent-1-en-1-yl-methyl)-1,7-dihydro-purin-6-one

30 (249) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-phenyl-2-oxo-ethyl)-1,7-dihydro-purin-6-one

- (250) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2-amino-phenyl)-2-oxo-ethyl]-1,7-dihydro-purin-6-one
- 5 (251) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2-acetylamino-phenyl)-2-oxo-ethyl]-1,7-dihydro-purin-6-one
- (252) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2-methylsulphonylamino-phenyl)-2-oxo-ethyl]-1,7-dihydro-purin-6-one
- 10 (253) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2-hydroxy-phenyl)-2-oxo-ethyl]-1,7-dihydro-purin-6-one
- (254) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-[2-(2-methoxy-phenyl)-2-oxo-ethyl]-1,7-dihydro-purin-6-one
- 15 (255) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-{2-[2-(ethoxycarbonylmethoxy)-phenyl]-2-oxo-ethyl}-1,7-dihydro-purin-6-one
- (256) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-{2-[2-(aminocarbonylmethoxy)-phenyl]-2-oxo-ethyl}-1,7-dihydro-purin-6-one
- 20 (257) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-{2-[2-(methylaminocarbonyl-methoxy)-phenyl]-2-oxo-ethyl}-1,7-dihydro-purin-6-one
- 25 (258) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-{2-[2-(ethylaminocarbonyl-methoxy)-phenyl]-2-oxo-ethyl}-1,7-dihydro-purin-6-one
- (259) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-{2-[2-(dimethylaminocarbonyl-methoxy)-phenyl]-2-oxo-ethyl}-1,7-dihydro-purin-6-one
- 30

(260) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(naphth-1-yl-methyl)-1,7-dihydro-purin-6-one

5 (261) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(isoquinolin-1-yl-methyl)-1,7-dihydro-purin-6-one

(262) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(quinazolin-2-yl-methyl)-1,7-dihydro-purin-6-one

10 (263) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(quinolin-4-yl-methyl)-1,7-dihydro-purin-6-one

(264) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(quinazolin-4-yl-methyl)-1,7-dihydro-purin-6-one

15 (265) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(2-phenylethyl)-1,7-dihydro-purin-6-one

(266) 8-[(2-aminoethyl)amino]-7-benzyl-1-methyl-2-benzylamino-1,7-dihydro-purin-6-one

20 (267) 8-[N-methyl-N-(2-aminoethyl)-amino]-7-benzyl-1-methyl-2-benzylamino-1,7-dihydro-purin-6-one

(268) 8-[N-ethyl-N-(2-aminoethyl)-amino]-7-benzyl-1-methyl-2-benzylamino-1,7-dihydro-purin-6-one

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(269) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-cyanophenyl)ethyl]-1,7-dihydro-purin-6-one

30 (270) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-aminocarbonyl-phenyl)-ethyl]-1,7-dihydro-purin-6-one

- (271) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-dimethylaminocarbonyl-phenyl)ethyl]-1,7-dihydro-purin-6-one
- 5 (272) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-methylsulphonyl-phenyl)-ethyl]-1,7-dihydro-purin-6-one
- (273) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[2-(2-methylsulphonylamino-phenyl)ethyl]-1,7-dihydro-purin-6-one
- 10 (274) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-methylsulphonylamino-ethyl)-amino]-1,7-dihydro-purin-6-one
- (275) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(2-phenylsulphonylamino-ethyl)-amino]-1,7-dihydro-purin-6-one
- 15 (276) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(naphth-1-yl-methyl)amino]-1,7-dihydro-purin-6-one
- (277) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(quinazolin-2-yl-methyl)amino]-1,7-dihydro-purin-6-one
- 20 (278) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(isoquinolin-1-yl-methyl)amino]-1,7-dihydro-purin-6-one
- 25 (279) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4,5-dimethyl-oxazol-2-yl-methyl)-1,7-dihydro-purin-6-one
- (280) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4,5-dimethyl-thiazol-2-yl-methyl)-1,7-dihydro-purin-6-one
- 30

(281) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(4,6-dimethyl-pyrimidin-2-yl-methyl)-1,7-dihydro-purin-6-one

5 (282) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-(pyrazin-2-yl-methyl)-1,7-dihydro-purin-6-one

(283) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(3-methyl-isoxazol-5-yl-methyl)-amino]-1,7-dihydro-purin-6-one

10 (284) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(4,5-dimethyl-oxazol-2-yl-methyl)-amino]-1,7-dihydro-purin-6-one

(285) 8-(3-amino-piperidin-1-yl)-7-benzyl-1-methyl-2-[(pyrazin-2-yl-methyl)-amino]-1,7-dihydro-purin-6-one
15

Example 2

Coated tablets containing 75 mg of active substance

1 tablet core contains:

20	active substance	75.0 mg
	calcium phosphate	93.0 mg
	corn starch	35.5 mg
	polyvinylpyrrolidone	10.0 mg
	hydroxypropylmethylcellulose	15.0 mg
25	magnesium stearate	<u>1.5 mg</u>
		230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone,
30 hydroxypropylmethylcellulose and half the specified amount of magnesium stearate.

Blanks 13 mm in diameter are produced in a tablet-making machine and these are then

rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

Weight of core: 230 mg

5 die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

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Example 3

Tablets containing 100 mg of active substance

Composition:

15 1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
20 magnesium stearate	<u>2.0 mg</u>
	220.0 mg

Method of Preparation:

25 The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

30 Diameter: 10 mm, biplanar, faceted on both sides and notched on one side.

Example 4

Tablets containing 150 mg of active substance

Composition:

5	1 tablet contains:	
	active substance	150.0 mg
	powdered lactose	89.0 mg
	corn starch	40.0 mg
	colloidal silica	10.0 mg
10	polyvinylpyrrolidone	10.0 mg
	magnesium stearate	<u>1.0 mg</u>
		300.0 mg

Preparation:

- 15 The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm. The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

- 20 die: 10 mm, flat

Example 5

Hard gelatine capsules containing 150 mg of active substance

25	1 capsule contains:	
	active substance	150.0 mg
	corn starch (dried) approx.	80.0 mg
	lactose (powdered) approx.	87.0 mg
	magnesium stearate	<u>3.0 mg</u>
30		approx. 420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

- 5 Capsule filling: approx. 320 mg
 Capsule shell: size 1 hard gelatine capsule.

Example 6

Suppositories containing 150 mg of active substance

10

1 suppository contains:

	active substance	150.0 mg
	polyethyleneglycol 1500	550.0 mg
	polyethyleneglycol 6000	460.0 mg
15	polyoxyethylene sorbitan monostearate	<u>840.0 mg</u>
		2,000.0 mg

Preparation:

- After the suppository mass has been melted the active substance is homogeneously
20 distributed therein and the melt is poured into chilled moulds.

Example 7

Suspension containing 50 mg of active substance

- 25 100 ml of suspension contain:

	active substance	1.00 g
	carboxymethylcellulose-Na-salt	0.10 g
	methyl p-hydroxybenzoate	0.05 g
	propyl p-hydroxybenzoate	0.01 g
30	glucose	10.00 g
	glycerol	5.00 g

70% sorbitol solution		20.00 g
flavouring		0.30 g
dist. water	ad	100 ml

5 Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution
10 and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 8

15 Ampoules containing 10 mg active substance

Composition:

	active substance		10.0 mg
	0.01 N hydrochloric acid q.s.		
20	double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

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Example 9

Ampoules containing 50 mg of active substance

Composition:

30	active substance		50.0 mg
	0.01 N hydrochloric acid q.s.		

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double-distilled water

ad 10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic
5 with common salt, filtered sterile and transferred into 10 ml ampoules.